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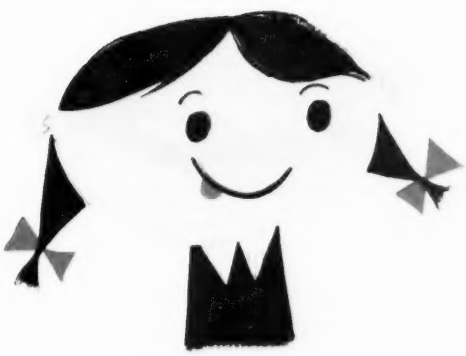

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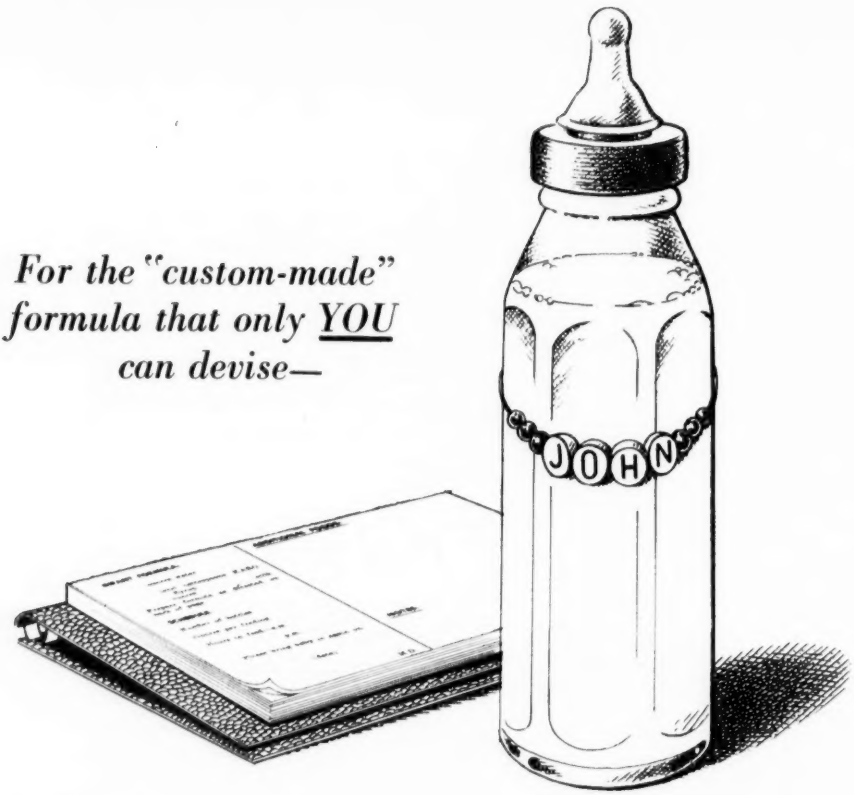

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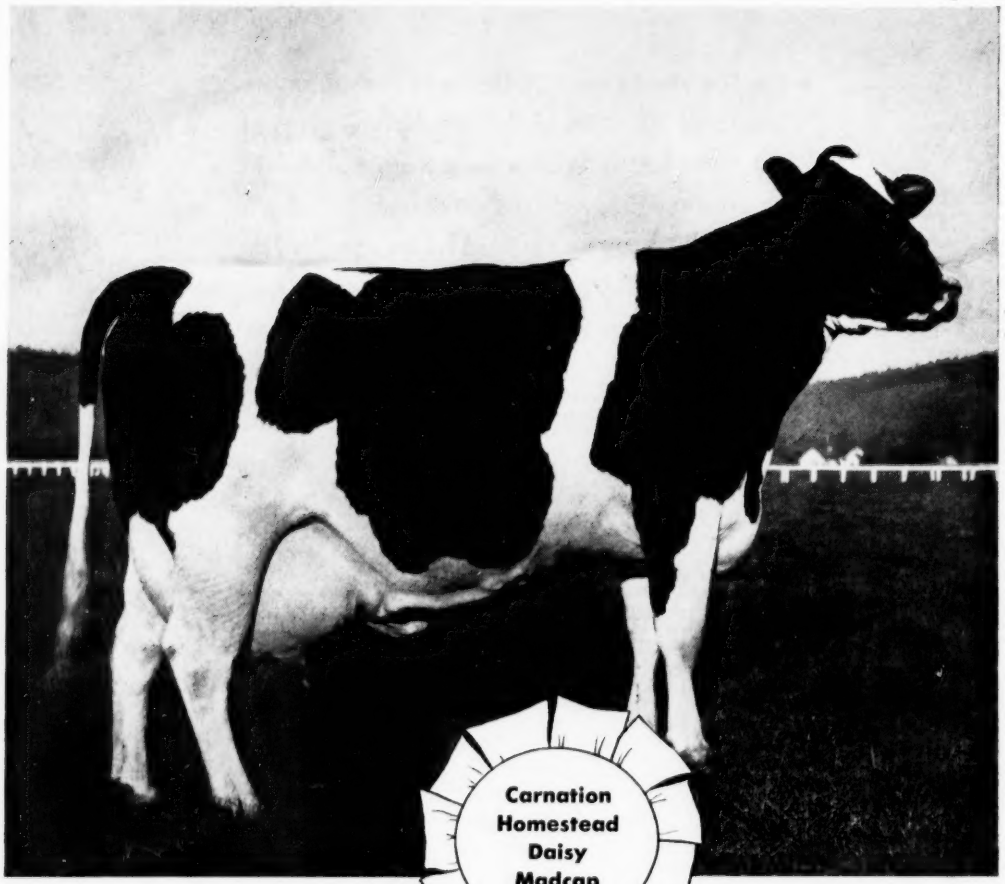

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THYMUS PROBLEM

J. T. LITTLETON, M.D.
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AND
S. P. PERRY, M.D.
SAYRE, PA.

DURING the past 346 years the thymus has many times been convicted and acquitted of causing obstructive symptoms and death in infants, children, and adults. Since 1858, when Friedleben first doubted Kopp's obstructive theory, there have been two sides to this argument, and the courts are still in session. It is the purpose of this paper to review the theories by which the thymus has been maligned, analyze their fundamental structure briefly, relate an experience of ours with reference to the current concepts of the thymus, present evidence against the obstructive theory, and to suggest a possible viewpoint to be taken by the physician when confronted with this problem.

Five principal theories have been proposed concerning how the thymus produces symptoms and death: The first, the obstructive theory by which the thymus produces mechanical pressure on the trachea, blood vessels, and nerves, principally the recurrent laryngeal and vagus. The second, advanced by Poultouf, in 1889, and later supported by Warthin and others, is that of status thymicolymphaticus, which ascribes death to a constitutional defect associated with hyperplasia of the thymus, especially the medulla, and a general lymphoid hyperplasia with hypoplasia of the adrenals and cardiovascular system. A third theory is anaphylaxis. A fourth describes death to an excessive and abnormal thymic secretion which results in a lymphotoxemia. The fifth suggests that death might be due to a hypersusceptibility to a physical and chemical agent.

The latter three theories have received little concrete experimental evidence to support them. We cannot disprove them, but hold them unlikely. Then let us direct our attention to the obstructive theory which was proposed by Kopp, in 1824. He described symptoms of stridor as due to pressure on the trachea by an enlarged thymus gland. This notion was accepted and magnified during the succeeding decades, particularly after the development of diagnostic roentgenology. It grew, however, on two misconceptions: the first, as to what is the normal roentgen anatomy of the infant's mediastinum; and the second, as to what are the normal dimensions and weight of the thymus at different ages.

Expiration films showing an engorged mediastinum were interpreted as representing thymic hyperplasia because of failure to appreciate the normal respiratory variations of the normal heart and mediastinum (Fig. 1). In any infant dying suddenly who demonstrated a thymus weighing over 15 gm. the gland was thought to

be hyperplastic, as compared with the then average normal-sized gland of about 7 gm. These early normal figures had been derived from autopsy specimens of infants dying of all causes. In 1927, Doctor Edith Boyd [1] proved the fallacy of these conclusions by demonstrating the rapidity with which a normal thymus involutes during acute illness and how markedly it does so in states of inanition. From glands of patients dying suddenly, before there was time for involution, she established normal weight curves for the thymus from birth through adolescence and arrived at values almost twice the previously accepted ones. Her predecessors had been comparing normal glands with abnormal ones. In 1921, Gerstenberger [2] first recognized the variation in the width of the normal mediastinum between full inspiration and full expiration and advocated phase films and fluoroscopy to evaluate the width

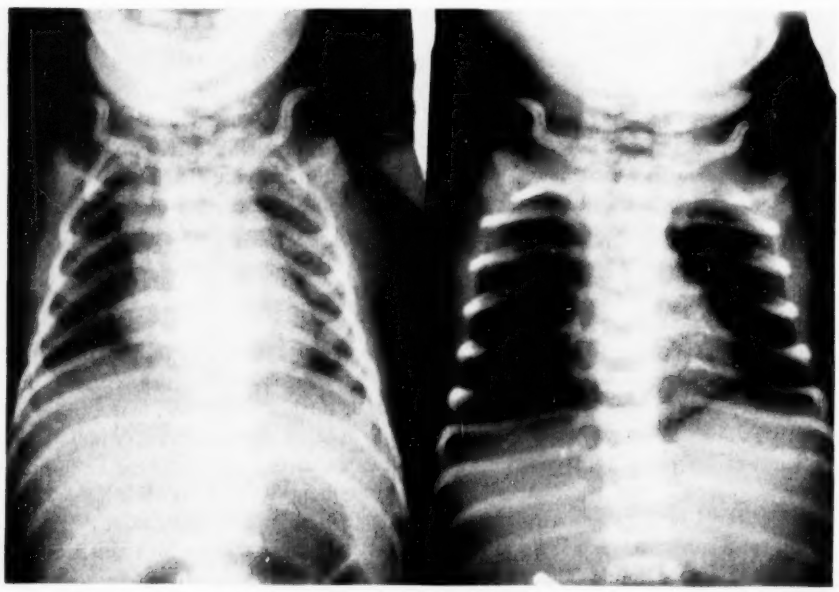

Fig. 1.—Erect films of the same patient made the same day. Full expiration on the left and full inspiration on the right. Such variations have many times been interpreted as representing reduction in the bulk of the thymus by radiation therapy.

of the mediastinum. Hasley,[3] in 1933, demonstrated this conclusively with the Jarre camera, taking as many as 100 films on a single patient. Translite tracings were made of all these films and were superimposed; no two were found to be identical in every phase. This was a significant finding. It proved that films before and after treatment were absolutely worthless and should never be used except for relative comparison. The outlines were disturbed by the cardiac cycle, the respiratory cycle,

1. Boyd, E.: Growth of the Thymus: Its Relation to Status Thymicolymphaticus and Thymic Symptoms, Am. J. Dis. Child. **33**:867-879 (June) 1927.

2. Gerstenberger, H. J.: Factor of Position of Diaphragm in Roentgen-Ray Diagnosis of Enlarged Thymus, Am. J. Dis. Child. **21**:534 (June) 1921.

3. Hasley, C. K.: Study of Motor Phenomenon of Mediastinum in Infants and Children, with Particular Reference to Hyperplasia of Thymus, Radiology **21**:477-484 (Nov.) 1933.

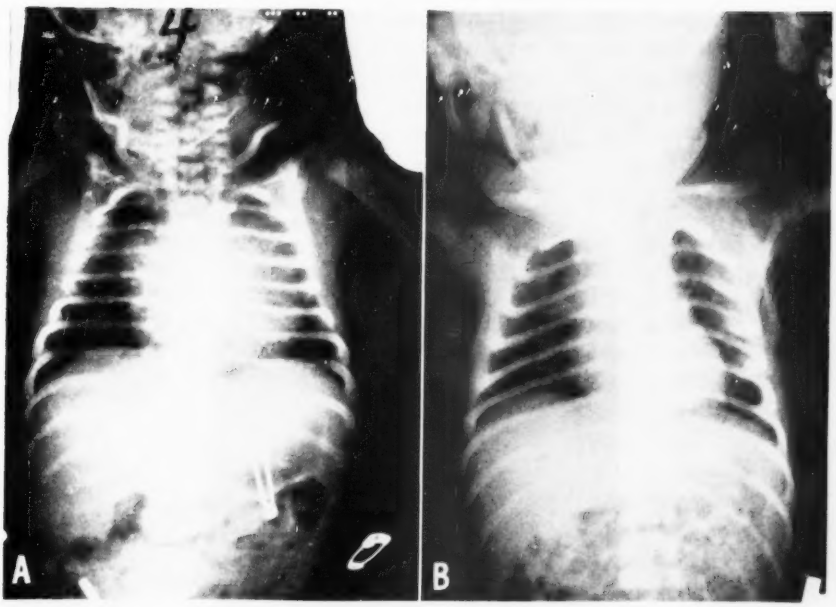

Fig. 2.—*A*, symmetrical widening of the mediastinum with visible right and left lobes of the thymus. Also called the fetal type. *B*, right lobe of the thymus visible. Called a "sail shadow" or "thymic notch."

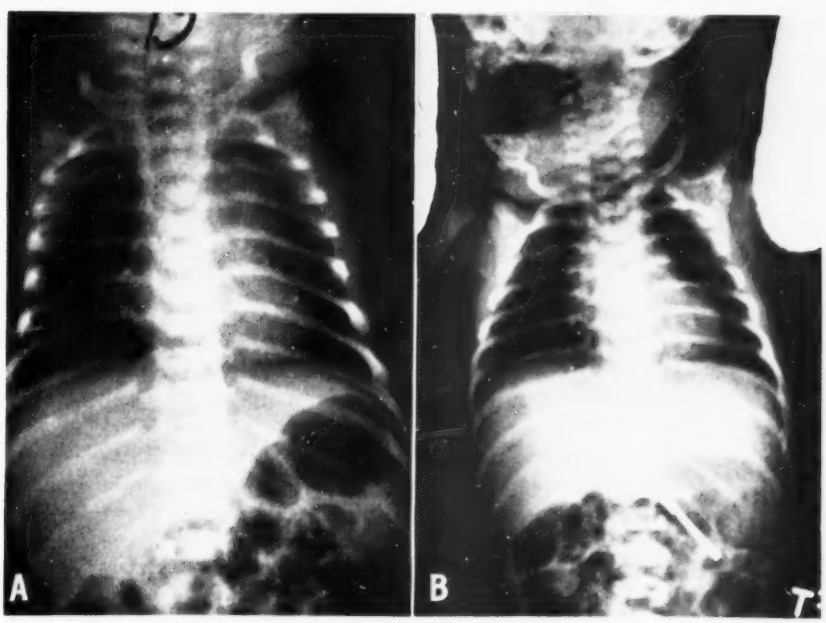

Fig. 3.—*A*, thymic notch, left side. *B*, long thin right lobe of the thymus.

the emotional state of the patient, and the movement of the liver. There was a striking shift of the mediastinum in the lateral position, at times to the right and then to the left, the shift occurring without any rhythm. An anteroposterior shift was noted, which suggested a possible circular or oval type of shifting of the mediastinum. On some of these films Hasley noted that the trachea was carried to one side, corresponding to the shift of the mediastinum, and that there was also a corresponding shift of the trachea in the cervical region. Lateral studies demonstrated a narrowing of the trachea during full inspiration, or during the time when the full length of the trachea was needed. Later studies have shown a buckling of the trachea during full expiration.

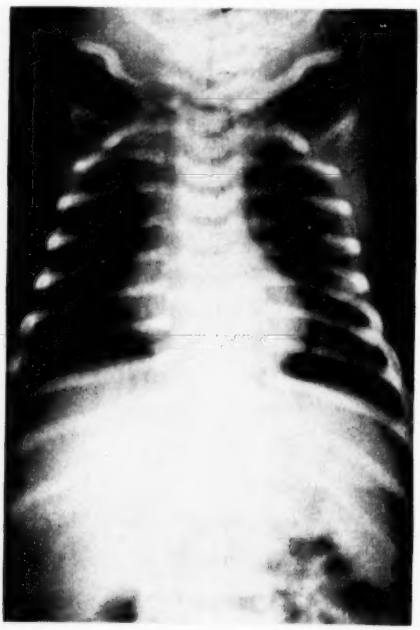

Fig. 4.—Visible right lobe with the major widening superiorly.

Caffey [4] demonstrated the many different roentgen appearances of the visible normal thymus, which are illustrated in Figures 2, 3, and 4 from our series; a symmetrical widening of the mediastinum, the right-sided thymic notch, the left-sided thymic notch, bilateral notches, the long thin thymus, and the major widening superiorly. These were all clinically normal asymptomatic babies. Noback [5] demonstrated the molding of the broad flat fetal thymus into the long narrow type by expansion of the lungs. Full molding takes place during the first four days of life. The normal transverse diameter of the infant's mediastinum became established at

4. Caffey, J.: Pediatric X-Ray Diagnosis: A Textbook for Students and Practitioners of Pediatrics, Surgery and Radiology, Chicago, Yearbook Publisher, Inc., 1945.

5. Noback, G. J.: Thymus in Newborn and Early Infancy, Radiology **7**:416-421 (Nov.) 1926.

2.5 to 3.0 cm. at the level of the lower border of the third thoracic vertebra. Our average figure for 600 babies was 2.78 cm. Hence, little by little we find that what was thought to represent an abnormal thymus is actually the normal anatomy and physiology of the infant mediastinum and that there are few reasons left for linking the thymus to compression symptoms.

Jackson is reported to have observed tracheal compression through the bronchoscope in 300 infants. This work has not been repeated.

Tracheal compression has never been satisfactorily demonstrated by roentgenographic means. Position of the head has been thought to lead to tracheal compression by the thymus; either by retraction of the trachea up into the sternal notch during extension of the head or by jamming the gland into the notch during expiration with elevation of the diaphragm. Crotti [6] describes in some detail retraction of the thymus into the sternal notch during extension of the head by the thyrothymic ligament. He believes that as the head extends, the diameter of the sternal notch is decreased and the gland pulled up into the sternal notch.

In an effort to reproduce this tracheal compression, a representative group of normal infants with visible thymus glands were examined by fluoroscope during extremes of flexion and extension of the head. The trachea was seen to elongate and narrow slightly during extension and to shorten and buckle during flexion, with some exaggeration of both these changes during inspiration and expiration. Never, however, was there sufficient narrowing of the trachea to produce respiratory embarrassment. In addition, approximately 30 infants were filmed in the lateral position during flexion and extension of the head; translite tracings of the films were made, and no tracheal compression was discovered (Figs. 5 and 6).

To further illustrate this point, iodized oil (Lipiodol) was instilled into the trachea of a cadaver, and these maneuvers were repeated (Fig. 7). It was interesting to note that, during extension, the point of motion of the cervical spine begins at the seventh cervical level, with no change in the position of the trachea or its relationship to the sternal notch or spine. If there is any motion of the soft tissue structures of the neck at this level and hence of the thymus, by retraction, then it must be very slight and certainly not enough to retract a large bulky gland into the sternal notch sufficiently to compress the trachea. In a second cadaver, the sternum was removed, and again in flexion and extension there is virtually no motion of the gland. In extreme flexion the trachea is displaced forward by pressure and shortened by buckling. One would think that it would be in this position that tracheal compression would develop, but this is highly improbable, since the gland must be displaced inferiorly. During inspiration the trachea is elongated and narrowed slightly, and during full expiration it is shortened and buckled. In no instance did we find any evidence of the gland being jammed into the sternal notch. As final evidence of these points, a 3-month-old baby, dying of unknown cause, was frozen within a few hours after death and sectioned longitudinally. The infant had a normal-sized cervicothoracic thymus (Fig. 8). The sagittal sections were then allowed to thaw sufficiently to permit full range of motion, and the head was put through the movements of full flexion and extension. Again, all motion begins at the seventh cervical vertebra, which is

6. Crotti, A.: Disease of the Thyroid, Parathyroid and Thymus, Ed. 3, Philadelphia, Lea and Febiger, 1938.

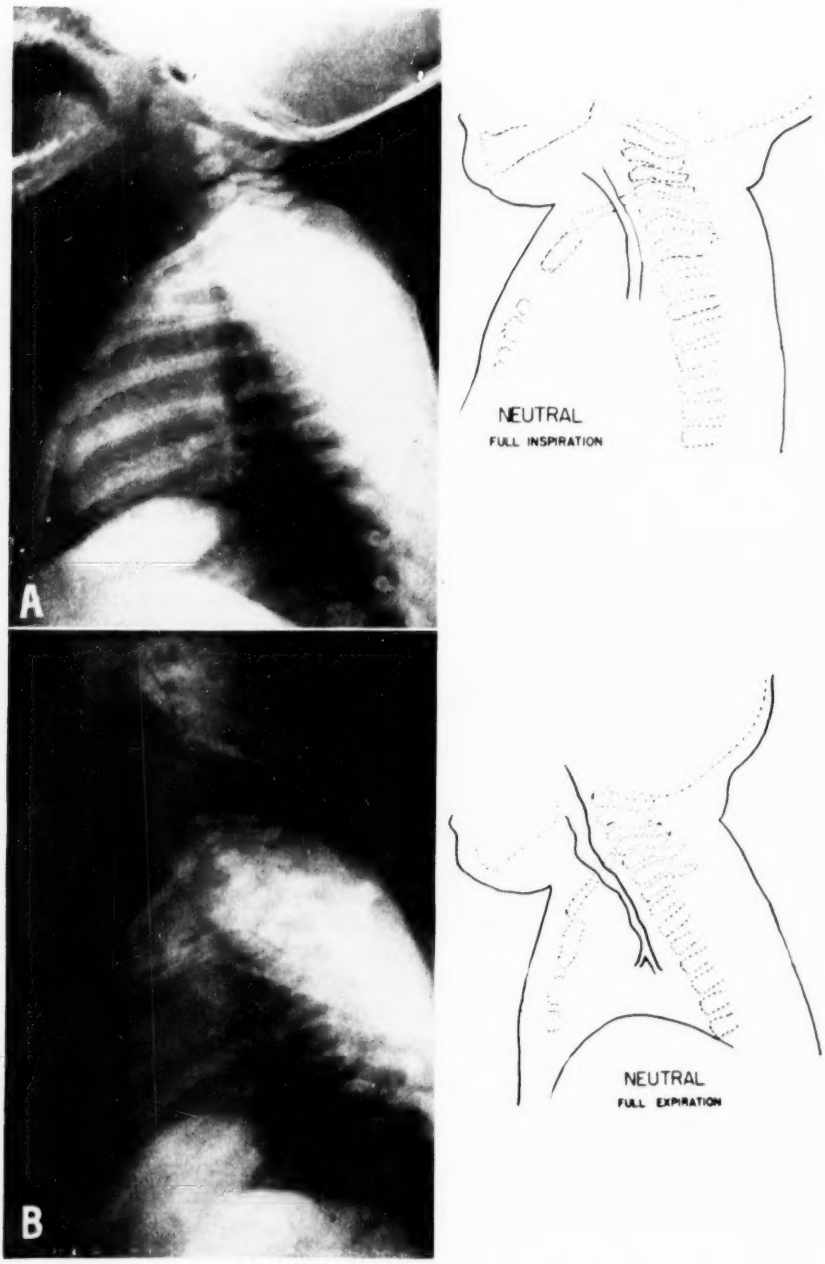

Fig. 5.—*A*, lateral erect film, neutral position, showing the tracheal airway. *B*, lateral view in full expiration demonstrating tracheal buckling.

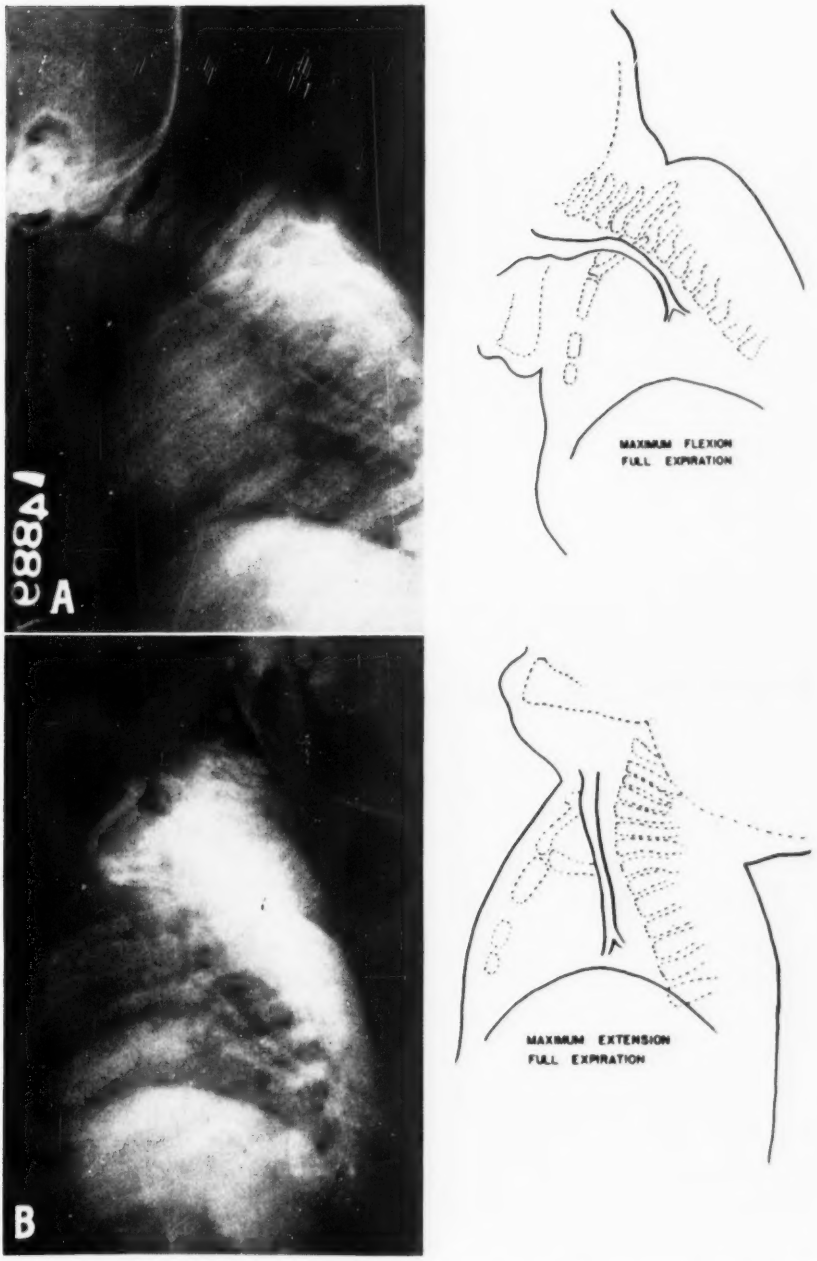

Fig. 6.—*A*, maximum flexion in full expiration without evidence of tracheal compression. *B*, maximum extension, full expiration, without significant change in the diameter of the trachea.

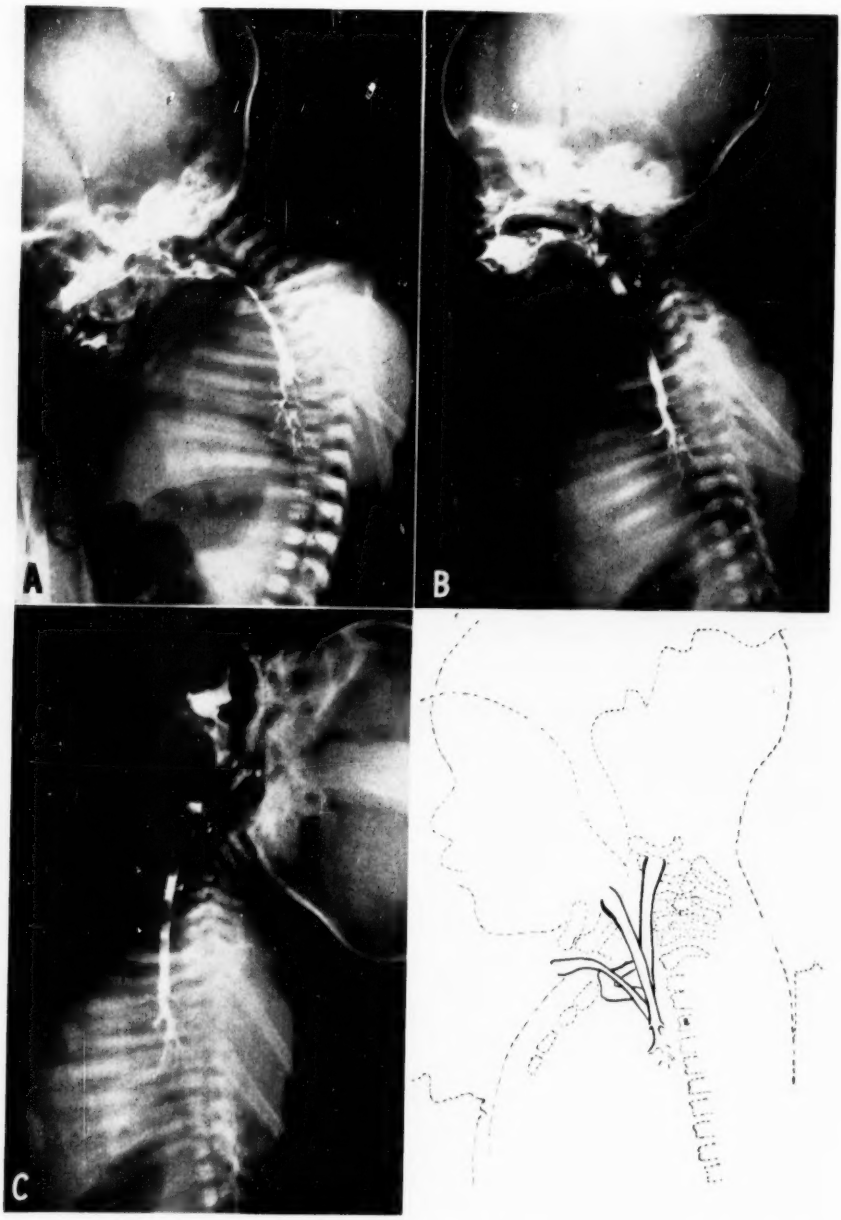

Fig. 7.—*A*, lateral view showing iodized oil (Lipiodol) instilled into the trachea, the head in forced flexion. The only change noted in the trachea is some shortening. *B*, neutral position, same specimen. *C*, forced extension without change in the diameter of the trachea. *D*, composite tracing of *A*, *B*, and *C*. Note that all of the motion in this soft, flaccid baby is at and above the seventh cervical level.

above the sternal notch, and even in this specimen, with a cervicothoracic thymus, there was no significant motion of the gland. Certainly there was no retraction of the gland into the neck. Also, there is no mention in the literature of vascular obstruction in infants showing supposed tracheal obstruction by an enlarged thymus. It can readily be seen from the section that the innominate artery, the left innominate vein, and even the aorta should be vulnerable to compression before the trachea is affected. On

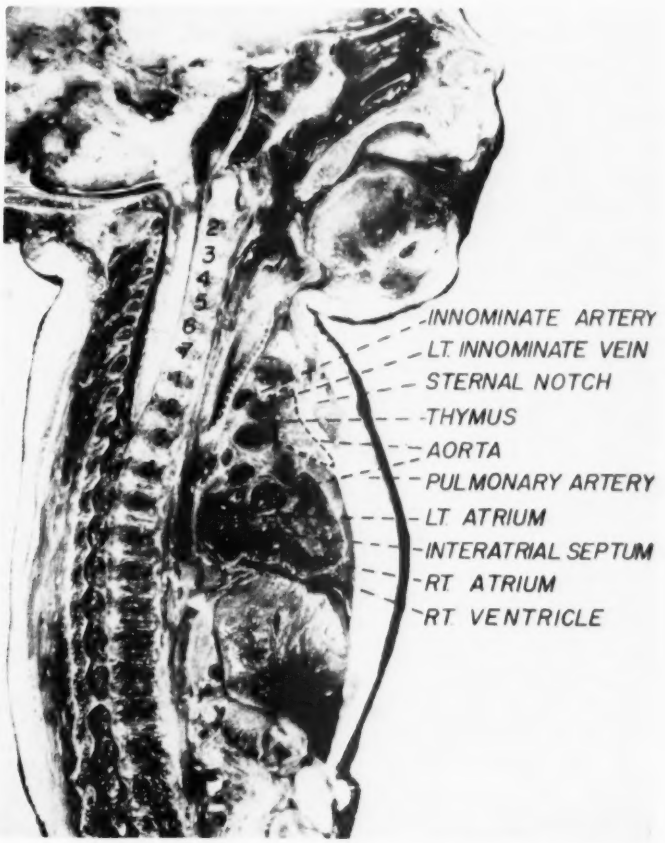

Fig. 8.—Sagittal midline section of 3-month-old infant. Note that the innominate artery, the left innominate vein, and the aorta are interposed between the thymus and the trachea. Also the uppermost level of this cervicothoracic thymus is at the level of the first thoracic vertebra below the level of motion of the cervical spine.

the basis of these findings it seems unlikely that position of the head or phase of respiration can lead to tracheal compression by a normally positioned thymus, no matter what its size.

Many autopsy descriptions have been published of infants dying of so-called thymic deaths by tracheal compression, but we have yet to read one which demonstrates actual tracheal compression by the gland. Vascular impressions have been noted on

the gland, but not tracheal impressions. In 1945, Carr [7] reported seven cases of death ascribed to asphyxia by thymic compression and demonstrated tracheal displacement but not tracheal compression.

There are numerous causes of stridor in infants which have definitely been shown not to be due to thymic compression. Some of these are as follows: congenital laryngeal stridor, which is probably the most common, due to an exaggeration of the infantile type of larynx with undue relaxation of the superglottic structures; congenital atony of the larynx; congenital atony of the vocal cords; stridor due to cerebral origin; bilateral abductor paralysis; neoplasm; tetany; subglottic diaphragm; tumors of the thymus (rare); lingual thyroid gland; retropharyngeal abscesses, and congenital flaccid tongue. There are a host of other conditions producing symptoms a supposedly enlarged thymus produces, of which atelectasis, stenosis of the trachea or larynx due to congenital heart conditions, whooping cough, and meningitis are the most common.

We have still not disproved the fact that an enlarged or abnormally positioned thymus gland can cause symptoms and/or death by tracheal compression, but in view of these considerations it must be exceedingly rare.

We have had no experience with status thymicolymphaticus, and the literature is voluminous. We wish simply to state the conclusions drawn by the Medical Research Council in conjunction with the Pathological Society of Great Britain and Ireland as reported by Young and Turnbull,[8] in 1931. They are as follows: "In the opinion of the Committee the facts elicited in the present inquiry are in harmony with those of Hammar (1926 and 1929) and Greenwood and Woods (1927) in affording no evidence that so-called 'status thymico-lymphaticus' has any existence as a pathological entity." Bromer [9] summarized the panel discussion on the thymus, conducted by the American Academy of Pediatrics, in 1938, as indicating that the members of the panel agreed that it would be well to discard the term status thymicolymphaticus, and if the thymus is in any way related to sudden death, it could only be in a secondary capacity; that roentgen therapy or extirpation of the gland would have no effect in preventing these sudden deaths. Boyd [1] examined the five cases reported by Poultouf in his original description of status thymicolymphaticus, and, though the weights of the glands were not given, the dimensions recorded were within the normal limits established by Von Sury. She thinks these five cases do not constitute adequate basis for considering the condition a new pathologic entity. Her final comment is that many of the accounts of death from status thymicolymphaticus would make excellent material for a Sunday magazine section.

Returning to our original five theories of thymic influence in disease or sudden death, we find the evidence is strong against all of them, and there is left little rational basis for the use of radiation therapy in the treatment of supposed thymic disorders either to reduce the bulk of the gland or to prevent status thymicolymphaticus.

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7. Carr, J. L.: Status Thymico-Lymphaticus, J. Pediat. **27**:1-43 (July) 1945.

8. Young, M., and Turnbull, H. M.: Analysis of Data Collected by Status Lymphaticus Investigation Committee, J. Path. & Bact. **34**:213-258 (March) 1931.

9. Bromer, R. S.: Diagnosis and Treatment of Thymic Hyperplasia, M. Clin. North America **26**:1,771-1,783 (Nov.) 1942.

Three years ago the radiology and pediatric services at the Guthrie Clinic and Robert Packer Hospital undertook to review the thymus problem under a grant established by the Edwards Memorial Fund. To date approximately 2,600 infants and children have been studied clinically and by roentgenogram to determine, if possible, the answers to the following questions: What is the normal anatomy of the infant mediastinum on roentgenogram? Can the thymus produce obstructive symptoms? How often is respiratory stridor due to tracheal compression by the thymus? When is radiation therapy indicated? To date our results have corresponded well with the findings in earlier studies, and we have added nothing new. This material has been presented in exhibit form to the Pennsylvania State Medical Society, the American Medical Association, the American Academy of Pediatrics, and the Radiological Society of North America with a rather surprising response. Many think, as we do, that the thymus has been unduly maligned as an etiological agent in the production of disease and death in infants. There are still, however, many general practitioners, pediatricians, and radiologists who hold firmly to the views of the 1920's that the thymus is responsible for the compression symptoms of infants and that all widened mediastinal shadows due to enlarged thymus are potential causes of death by tracheal compression and should all be treated. Others think that if tracheal compression can be demonstrated in lateral views, at fluoroscopy, or in roentgenograms, the thymus should be treated by x-ray, irrespective of its size in the anteroposterior views. Some believe that all infants with respiratory symptoms and a widened mediastinal shadow should receive at least token radiation therapy to insure the practitioner against medicolegal action. This line of reasoning has led to a vicious circle. The mother presents her baby to the family doctor because of an inspiratory stridor and perhaps bouts of cyanosis. The doctor can find nothing to account for the symptoms save a widened mediastinal shadow. To protect himself, he asks the pediatrician to see the baby with reference to radiation therapy, which often has been requested by the parent. The pediatrician, after study, confirms the referring physician's findings, but is reluctant to assume such responsibility and refers the child to the radiologist. He, in turn, reviews the films, examines the child by fluoroscope, often believes the mediastinum to be normal, but still gives some therapy to protect himself and to satisfy the parent, the doctor, and the pediatrician. These, you will admit, are rather poor reasons for administering radiation therapy. Some clinics reported treating from one to three infants per week, and one radiologist as many as seven a week. We are certain that hundreds of babies in this country still are receiving annually needless radiation therapy for widened mediastinal shadows. A real problem still exists in the management of the child with the so-called thymic syndrome.

There is, however, within this chaos of thymic obsession, one striking feature about the use of radiation therapy on these children, and undoubtedly this is the reason why many men still use it. The child with repeated bouts of stridor, cough, and cyanosis is benefited by therapy, and often dramatically so. Such case reports are common in the thymus literature and have frequently been reported to us by doctors who viewed the exhibit. This has happened too frequently to be overlooked. We doubt if the cause and effect are in and on the thymus, but should prefer to think that there is an underlying inflammatory disease of the trachea and bronchi which, by mucosal edema, excessive mucoid secretion, and, perhaps, tracheal stenosis pro-

duce the symptoms of stridor, cough, and cyanosis and that it is these structures which are affected by therapy rather than the thymus, which is just along for the ride. In 1930, Pancoast and Pendergrass [10] demonstrated tracheal narrowing by edema in acute tracheitis and later stenosis. Attention has been focused on the thymus too long. If we forget the thymus and study these children bacteriologically at bronchoscopy, as well as clinically, it may well be possible to establish definite criteria for treatment of these children. Certainly we occasionally see dramatic results with radiation therapy in asthma, and perhaps this is a similar mechanism.

We believe the physician's viewpoint, when confronted with the problem of a child with stridor, cough, and cyanosis should be a conservative one along the following lines. There should be a complete clinical study to include fluoroscopy and anteroposterior and lateral films of the chest, including the upper respiratory tract. Inspiration and expiration films should be made if a foreign body is suspected. These are quite simple to make if the child can be made to cry lustily, and most of them need no urging. Blood cell counts, sedimentation rate, and throat cultures are important to exclude infection; an ear, nose, and throat survey is important to exclude congenital anomalies. An allergy survey should also be made. If these do not provide the answer (and in all of our cases it has) then perhaps symptomatic radiation therapy would be indicated—but not with any thought of effect on the thymus.

SUMMARY

There is little concrete evidence to support any of the five theories linking the thymus gland to symptoms of stridor, cough, and cyanosis or to sudden death.

These facts are not generally appreciated, and many practitioners, pediatricians, and radiologists are still treating widened mediastinal shadows and symptoms of cough, stridor, and cyanosis with radiation therapy.

We think that by having kept attention finely focused on the thymus, we may well have overlooked a definite clinical entity of low-grade, chronic, or recurrent tracheobronchitis which is best managed or at least aided by roentgen therapy.

Dr. Phillip B. Armstrong, Department of Anatomy, Syracuse University, identified the structures in the sagittal section; Dr. W. H. Allen, Department of Pediatrics, the Guthrie Clinic, gave assistance in the early phases of this study.

10. Pancoast, H. K., and Pendergrass, E. P.: Roentgenologic Diagnosis of Diseases of Upper Respiratory Tract in Children, Am. J. Roentgenol. **23**:241-264 (March) 1930.

BROMIDES IN THE TREATMENT OF EPILEPSY IN CHILDREN

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BROMIDES were the first effective treatment for epilepsy. Sir Charles Locock [1] reported on their use in epilepsy in 1853, and for many years they were widely used. Today, however, because of the enthusiasm for the newer anticonvulsant drugs, bromides are not used very extensively. Some physicians even consider bromides to be of historical interest only. Several recent reviews on the treatment of epilepsy mentioned the past importance of bromides and then dismissed the drugs as "ineffective" and "possessing many undesirable side reactions." [2] In this clinic bromides are still considered to be a valuable anticonvulsant. Since this appears to be contrary to the prevailing opinion, it seems worth while to report our experience with the use of bromides in the treatment of epilepsy in children.

MATERIAL AND METHODS

Selection of Patients.—A total of 196 epileptic children with severe organic brain lesions evidenced by mental retardation, hemiplegia, or other gross neurological changes were treated with bromides for periods of two years or longer. Of these children, 102 had been previously treated with anticonvulsants without success. Ninety-four had received no previous anticonvulsant drugs.

Dosage and Administration.—The preparation used contained equal amounts of sodium, potassium, and ammonium bromide.[3] The optimal dosage varied for different children. This could be ascertained only by trial. The average initial and maximum doses found to be satisfactory were as follows:

Age, Yr.	Daily Initial Dosage	Daily Maximum Dosage
Under 6	0.3 gm. (5 grains) 2 times	0.6 gm. (10 grains) 3 times
Over 6	0.3 gm. (5 grains) 3 times	1 gm. (15 grains) 3 times

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1. Radcliffe, C. B.: Lectures on Epilepsy, Pain and Paralysis and Certain Other Disorders of the Nervous System, Philadelphia, The Blakiston Company, 1866.

2. Merritt, H. H., and Carter, S.: Anticonvulsant Drugs, M. Clin. North America **34**:341 (March) 1950. Lennox, W. G.: Therapeutic Agents in the Treatment of Epileptiform Seizures: Advances in Pediatrics, Chicago, The Year Book Publishers, Inc., 1948, Vol. 3. Forster, F. M.: Medical Therapy of Epilepsy, Neurology **1**:153 (March-April) 1951. Perlstein, M. A.: Newer Drugs in the Therapy of Epilepsy, Illinois M. J. **99**:75 (Feb.) 1951.

3. The formula is as follows:

Ammonium bromide	40 gm.
Potassium bromide	40 gm.
Sodium bromide	40 gm.
Amaranth solution	3 cc.
Compound benzaldehyde elixir to make	1,000 cc.

Each teaspoonful (5 cc.) of this mixture contains 0.6 gm. (9 grains) of total bromides.

Each patient was given the daily initial dose, and the amount of bromides was then increased until the seizures were controlled or there was evidence of oversedation. In general, a good therapeutic effect was obtained when the blood bromide concentration ranged between 14.5 and 24.3 mEq. per liter (116 and 194 mg. per 100 cc.). In some patients bromide levels as high as 34 mEq. per liter were necessary to obtain a satisfactory clinical response; in others control was achieved with levels as low as 10 mEq. per liter.[4]

Bromide therapy was found to be most effective when there was a fairly constant and moderate intake of table salt (NaCl), since the intake of sodium chloride diminishes the retention of bromide, the bromide ion being replaced in the blood by the chloride.[5] Salt used in the cooking and serving of food should be restricted. When there is unusual salt loss, as from vomiting or excessive perspiration, the bromide intake must be reduced or temporarily discontinued. At such times it is wise to substitute one of the other anticonvulsants, such as phenobarbital. Since bromide excretion is almost entirely by way of the kidney, renal damage or reduced urinary flow contraindicates its administration.

RESULTS

For the purpose of this study, improvement was scored as follows:

1. Controlled—when no seizures occurred during the observation period of two years

2. Markedly improved—when the number of seizures was reduced to less than one-fourth of the previous frequency

TABLE 1.—*Results of Bromide Therapy in 196 Children with Seizures Associated with Severe Organic Brain Lesions*

Type of Spell	No. of Patients	Controlled	Markedly Improved	Improved	Failure
Major motor	71	22	16	7	26
Minor motor	38	14	8	3	13
Mixed	73	24	13	4	32
Others	14	1	2	1	10
Total	196	61	39	15	81

3. Improved—when the incidence of seizures became less than half the previous total

4. Failure—when the number of seizures was only slightly reduced or remained unaltered

Seizures were classified as follows:

Major motor—typical grand mal seizures, generalized or focal

Minor motor—myoclonic jerks and akinetic attacks of short duration

Mixed—in which both major and minor motor seizures were present

Others—psychomotor attacks, atypical major or minor motor seizures, petit mal of simple staring type (3-per-second spike-and-wave dysrhythmia)

As shown in Table 1, seizures were completely controlled with bromides alone in 61 (31%) of the 196 patients. In an additional 39 (20%) the seizures were reduced to less than one-fourth of their previous frequency. Although only 51% of

4. Lysaught, J. N.; Crigler, J. F.; Livingston, S., and Laslo, K.: The Use of Bromides in the Treatment of Organic Epilepsy in Children: The Determinations of Blood and Cerebrospinal Fluid Bromide Levels in Treated Patients, unpublished data.

5. (*a*) Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, The Macmillan Company, 1945. (*b*) Wallace, G. B., and Brodie, B. B.: The Distribution of Administered Bromide in Comparison with Chloride and Its Relation to Body Fluids, J. Pharmacol. & Exper. Therap. **65**:214 (Feb.) 1939. (*c*) Palmer, J. W., and Clarke, H. T.: Elimination of Bromides from the Bloodstream, J. Biol. Chem. **99**:435 (Jan.) 1933.

the 196 patients received marked benefit from bromide therapy, it must be emphasized that these were all patients with severe organic epilepsy, and the majority had not been helped by the newer anticonvulsants (Table 2).

UNTOWARD DRUG REACTIONS

It has been our experience that infants and children tolerate bromides well, and that toxicity is negligible when the administration is carefully supervised. The common untoward reactions reported from bromide administration are skin rashes, mental and neurological disturbances, and gastrointestinal symptoms such as anorexia, constipation, and gastric distress.[5a]

Drowsiness and acneiform skin eruptions were the only untoward reactions observed in this group of patients. Psychoses and neurological manifestations reported in adults receiving bromides were not observed. We did not encounter a single "drug rash" in any child prior to puberty. Acne appeared only in adolescence. Drowsiness was seen when large doses of bromides were used, but rarely occurred until the blood bromide level exceeded 20 mEq. per liter. There was no absolute

TABLE 2.—*Results of Bromide Therapy in 102 Children with Seizures Associated with Severe Organic Brain Lesions in Whom Anticonvulsant Treatment Had Failed**

Type of Spell	No. of Patients	Controlled	Markedly Improved	Improved	Failure
Major motor	38	10	7	3	18
Minor motor	17	8	5	2	2
Mixed	41	10	6	1	24
Others	6	0	1	1	4
Total	102	28	19	7	48

* Anticonvulsants used included phenobarbital diphenylhydantoin (Dilantin), Mesantoin (hydantoin derivative), trimethadione (Tridione), and mephobarbital (Mebaral).

correlation between the blood-bromide level and the appearance of toxic reactions. Children in good physical condition tolerated extremely high levels without apparent mental impairment.

The margin of safety in bromide therapy appears to be considerable. This is an important consideration, as many physicians are not in a position to make blood-bromide determinations. Acute bromide poisoning rarely occurs, since an amount sufficient to raise the blood bromide to a toxic level could hardly be ingested without vomiting.[5c] Death from bromidism, without complicating factors such as chronic renal or heart disease, must be exceedingly rare. Goodman and Gilman [5a] state that bromide concentrations in the serum as high as 400 mg. per 100 cc. (50 mEq. per liter) have occurred, but these unusually high levels are not long compatible with life. However, a partial review of the literature revealed a number of reports in which bromide levels of 50 to 59 mEq. per liter were found in adults, with recovery.[6] We have recently observed two children in whom levels of 51 and 48.8 mEq. per liter, respectively, were found. Both had uneventful recoveries.

6. Detweiler, H. K.: Bromide Intoxication, Canad. M. A. J. **48**:309 (April) 1943. Campbell, J. D.: Bromide Intoxication: Report of 36 Cases, South M. J. **42**:967 (Nov.) 1949. Sensenbach, W.: Bromide Intoxication, J. A. M. A. **125**:769 (July 15) 1944.

CONCLUSIONS

Bromides constitute a valuable anticonvulsant for the treatment of seizures associated with severe organic brain lesions. In children, bromides are relatively free of untoward effects. Certainly they cause none of the dangerous reactions found in some of the newer anticonvulsants. The cost of bromides is a fraction of that of the newer drugs. This is an important consideration in a condition requiring prolonged medication. In the treatment of a condition as heterogeneous and as variable in its response to therapy as epilepsy, the physician needs to include in his armamentarium all the effective anticonvulsants. Knowledge of the types of epilepsy and of the drugs known to be most effective in each is essential. For each patient, the probable effectiveness of the available agents must be weighed against the possible toxic effects.

SUMMARY

Bromides are an effective and useful anticonvulsant for treatment of epilepsy associated with organic brain lesions.

Common side-effects of bromide administration in adults—acneiform rashes and mental and neurologic changes—are seldom seen in infants and preadolescent children.

Bromides as anticonvulsants possess a wide margin of safety.

POSTPRANDIAL HYPOLIPEMIA OF PANCREATIC FIBROCYSTIC DISEASE

A Diagnostic Test

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THE CHIEF pathologic changes of fibrocystic disease or fibrosis of the pancreas, according to Andersen [1] and others [2] are (1) replacement of the acini of the pancreas by epithelium-lined cysts embedded in fibrous tissues but without changes of the islets of Langerhans; (2) bronchitis, bronchiectasis, abscesses, and bronchopneumonia of the lungs; (3) symptoms of vitamin-A deficiency in children who die within the first year of life, and, occasionally, (4) atresia of the small bowel or the cystic or pancreatic ducts. The cause of the pancreatic lesion is not known, but probably it is present at birth.

The symptoms of these patients are comparable to those observed in dogs following ligation of the pancreatic duct and can be ascribed [3] to the absence of the external secretion of the pancreas. The symptoms of the disorder in infants and children are related to the gastrointestinal tract and to the respiratory system. Periodic vomiting and a nonliquid diarrhea in infants or young children and failure to gain or maintain weight are associated with symptoms of infection of the lungs. The stools are bulky, pale, putrefactive, and fatty, but without exudates or blood. Under favorable circumstances and with appropriate diet the symptoms sometimes disappear for several months. Fat foods, especially, are not tolerated by patients with fibrocystic disease; proteins and carbohydrates are the main nutritive substances in the diet. Manifestations of vitamin-A deficiency are due probably to failure to absorb the vitamin, and the associated osteoporosis is caused by this deficiency or deficiency of calcium salts or both. Fatty changes of the liver and the occasional lymphocytic infiltration of the intestinal mucosa are considered to be secondary.

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The Seymour Coman Fellow in Pathology of the University of Chicago, The School of Medicine (Miss Carbonaro).

From the Henry Baird Favill Laboratory and the Pediatric Service of St. Luke's Hospital, and the Department of Pathology of the University of Chicago, The School of Medicine.

1. Andersen, D. H.: Am. J. Dis. Child. **56**:344-399, 1938.
2. Farber, S.; Shwachman, H., and Maddock, C. L.: J. Clin. Invest. **22**:827-838, 1943.
3. Shohl, A. T.; May, C. D., and Shwachman, H.: J. Pediat. **23**:267-279, 1943.

Pediatricians need to distinguish between fibrocystic disease and other disorders of nutrition which clinically are diagnosed as celiac disease. Andersen stated that the term celiac disease designates a clinical syndrome, not a disease entity, and that it may be produced by two or more diseases, one of which is cystic fibrosis of the pancreas.

Since fibrocystic disease of the pancreas results in destruction of the acinar tissues and a loss or decrease of their physiologic functions, the clinical diagnosis can be difficult, especially before the symptoms of pulmonary lesions appear. Theoretically, according to Andersen, the most direct method for the diagnosis of pancreatic deficiency is the assay of pancreatic enzymes in the duodenal fluids. The assay of trypsin, in her opinion, is a reliable means for diagnosis of pancreatic deficiency because it is uniformly low or absent in this disorder. The assay of amylase is not reliable because of its low concentration during the first months of infancy and in many older infants and young children with chronic diarrhea. Amylase may be present occasionally in patients with pancreatic fibrosis, presumably because salivary amylase is not destroyed during its passage through the stomach. Lipase is present in normal infants of all ages and its concentration is reduced in congenital pancreatic deficiency. However, the assay of lipase is less reliable for diagnostic purposes because of low values in an occasional control case and because of technical difficulties. The determination of serum amylase has no value in congenital pancreatic deficiency.

This discussion of the assay of duodenal secretions for trypsin, lipase, and amylase activity leaves the impression that the assay of trypsin in aspirated duodenal fluids is the best method for establishing normal or abnormal pancreatic secretion. Difficulties in obtaining the duodenal fluids for assay have led to indirect methods for the estimation of tryptic activity in the bowel by measurements of the amino-acid (glycine) content of the blood following the ingestion of gelatin or casein, preferably the gelatin. West, Wilson, and Eyles [4] observed in infants or children with fibrocystic disease that the blood aminonitrogen remained close to the fasting level for a considerable time after the ingestion of 1.5 gm. gelatin per kilogram of body weight. Occasionally it rose slightly after three to five hours. The difference in response to this protein meal in infants and children with normal functions and in those with cystic fibrosis of the pancreas was sufficiently great and constant, in their opinion, to be a specific diagnostic test for the disease. Anfanger and Heavenrich [5] substantiated their conclusion. Children with little tryptic activity of their duodenal fluid, tested with a gelatin meal by Christensen and Shwachman,[6] had a rise of blood glycine not exceeding 2.5 times the fasting level, and those with good pancreatic enzyme activity had a large increase, an average of 5 times. Inconsistent results were observed in several patients.

The estimation of vitamin A in the blood following ingestion as an indirect measure of lipase activity of the pancreas secretions also has been used in the detection of fibrocystic disease of the pancreas. The characteristic curve according to

4. West, C. D.; Wilson, J. L., and Eyles, R.: Am. J. Dis. Child. **72**:251-273, 1946.

5. Anfanger, H., and Heavenrich, R. M.: Am. J. Dis. Child. **77**:425-436, 1949.

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Abbott, McCreary, Pocock, and Brown [7] in an untreated patient has a low fasting level with little or no rise during a three- to seven-hour interval of observation. When the water-soluble form of the vitamin was given, these authors found a normal absorption curve. In celiac disease a low curve with both preparations was observed. Elghammer, Reichert, and Philipsborn [8] considered the vitamin-A-absorption curve valuable in the study of both fibrocystic disease and celiac disease, but chose to evaluate the lipase activity of the pancreatic secretion by an estimation of the chylomicrons (particles of lipid in transport) of the blood. This they did by dark-field examination of capillary blood obtained by needle puncture from the finger and by counting the chylomicron particles in a ruled 1-mm. square field placed in the ocular of the microscope. Normal curves were established with 22 children aged 6 weeks to 3 years. The children had had no food for 12 to 15 hours, the small infants for 8 to 10 hours, and then they were given by mouth or gavage 30 cc. of cream per kilogram of body weight, not exceeding 120 cc. The chylomicrons of

TABLE 1.—*Normal Group*

		Blood Esterified Fatty Acids, mEq./L.			
Age	Sex	Fasting Level	3 (or 4) Hr.	5 (or 6) Hr.	% Increase
8 wk.	M	10.0	13.2	12.0	32.0
14 mo.	M	8.4	11.8	15.0	79.7
14 mo.	F	9.0	20.4	18.3	126.6
23 mo.	F	13.8	19.3	22.8	65.2
18 mo.	M	9.7	21.5	15.5	121.6
21 mo.	F	11.8	19.6	16.8	66.1
34 mo.	M	8.4	18.5	15.6	120.2
31 mo.	M	10.7	31.7	21.0	196.2
3 yr.	M	7.2	16.5	14.2	56.3
5 yr.	M	12.2	19.3	19.3	58.0
7 yr.	M	7.2	11.4	12.7	76.4

the blood were counted at hourly intervals for four hours. After the meal in the normal children the number of chylomicrons increased to reach a maximum about three hours later and then diminished. Plotted, the results formed a curve like that observed by Hirsch and Carbonaro [9] in their studies of the esterified fatty acids of the blood in the postprandial lipemias of human adults. Then 10 children with gastrointestinal disturbances were tested. Of these, eight had fibrocystic disease. The results of the chylomicron counts of these fibrocystic-diseased patients when plotted formed a straight line close to and parallel with the base line. In other words, there was no postprandial increase in the number of chylomicrons of the blood with fibrocystic disease. This demonstrated a lack of fat absorption from the bowel and reflected the deficient pancreatic enzyme activity.

Studies of the esterified fatty acid content of the blood during the postprandial hyperlipemia of normal human adults and of diabetics suggested that this method could be applied diagnostically to measure pancreatic function in children and to disclose the deficiency with fibrocystic disease. A sample of blood was drawn at

7. Abbott, V.; McCreary, J. F.; Pocock, R., and Brown, A.: Canad. M. A. J. **64**:419-423, 1951.

8. Elghammer, W. R.; Reichert, J. M., and Philipsborn, H. F., Jr.: Pediatrics **5**:621-625, 1950.

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the so-called fasting level in the morning. Then 36% cream was given by mouth in an amount calculated at 4 gm. fat per kilogram of body weight. Samples of blood were drawn three or four hours later and again six hours later. The esterified fatty acids of the blood were determined according to the method of Bauer and Hirsch.[10] The results obtained with the normal group are collected in Table 1. The percentage increase of the maximum postprandial elevation of the esterified fatty acids in this group of 11 normal children ranged between 56.3 and 196.2, excepting the infant of 8 weeks who had an increase of 32.0%. Comparable postprandial variations have been observed in normal human adults.[9] Clearly the absorption of fat from the intestinal tract as measured by these analyses reflects adequate digestive (pancreatic) functions for fats.

In contrast, the results of the fat-tolerance tests (Table 2) in children of families with fibrocystic disease demonstrate that those with fibrocystic disease have slight

TABLE 2.—*Familial Fibrocystic Disease*

Age, Yr.	Sex	Blood Esterified Fatty Acids, mEq./L. Fasting Level	3 (or 4) Hr.	5 (or 6) Hr.	% Increase	Comment
			Family A			
2.....	F	5.9	6.4	5.4	8	Fibrocystic, living
3.....	F	7.4	7.4	7.4	0	Fibrocystic, living
		7.2	8.0	8.0	11	
		5.7	6.1	5.4	7	
			Family B			
9/12.....	M	11.1	11.8	11.4	6	Fibrocystic, living
		8.8	8.8	6.0	0	
6.....	M	10.7	33.3	19.8	211.2	Normal
			Family C			
9/12.....	F	9.0	8.7	9.0	0	Fibrocystic, died; no necropsy
5.....	F	4.9	5.4	4.9	9	Fibrocystic, died; necropsy
7.....	M	3.9	4.7	4.2	20.5	Fibrocystic, living
3.....	M	4.5	9.2	8.4	104.4	Normal
3.....	M	6.3	19.6	...	211.1	Normal
5.....	F	7.4	13.8	10.9	86.4	Normal

or no postprandial increase of the esterified fatty acids of the blood. Both children in Family A had the clinical features of fibrocystic disease, and the results of the three separate tests on the second child were practically the same. The results in the children of Families B and C distinguish clearly the ones with fibrocystic disease from those without. The one child with fibrocystic disease in Family B had no postprandial increase of the esterified fatty acids of the blood, whereas the other without evidence of the disease had a high normal value. The results in the six children of Family C are also striking. The first two died, and the necropsy on the body of the second demonstrated the tissue changes of fibrocystic disease. The third child, still living, has the clinical symptoms of the disease, and the test demonstrates a markedly reduced postprandial lipemia. The other three, two of them twins, have the normal postprandial percentage increase of the esterified fatty acids of the blood.

10. Bauer, F. C., Jr., and Hirsch, E. F.: Arch. Biochem. **23**:137-140, 1949.

SUMMARY

The esterified fatty acids of the blood at the so-called fasting level in normal children aged 8 weeks to 7 years ranged between 7.2 and 13.8 mEq. per liter. The postprandial increase following a 4 gm. fat per kilogram test meal (36% cream) ranged in these children to as much as 31.7 mEq. per liter. Excepting the 32% increase in the infant, the percentage increase among the children varied from 56.3 to 211.2%.

In children with fibrocystic disease there is only a slight or no postprandial increase of the esterified fatty acids of the blood, indicating a marked failure of fat absorption from the bowel and reflecting a markedly decreased pancreatic function.

A test meal (36% cream) of 4 gm. fat per kilogram of body weight given to children by mouth with estimations of the esterified fatty acids of the blood at the fasting, the four-hour, and the six-hour postprandial levels affords a convenient laboratory test for evaluating pancreatic functions in children with or suspected to have fibrocystic disease.

PSYCHOGENIC VOMITING IN CHILDREN

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VOMITING may be the first indication of an emotional disorder in an infant or child and in some cases is the only obvious symptom. A review of the general medical literature reveals that there are very few reports dealing with this topic. References to it in the psychiatric literature are more common, but here again the subject is covered in a rather sketchy manner. English and Pearson [1] indicate that there are several mechanisms responsible for vomiting in children. They indicate that repressed hostility may be one reason. They also point out that identification with a pregnant mother may be a cause for vomiting in girls. An identification with an ill parent and a desire to be like the parent may be a third reason for vomiting. A fantasied ingestion of a love object may be the fourth reason. Bettelheim [2] cites a case of a boy whose parents forced him to eat. This boy vomited as an expression of hostility towards his parents. Kanner [3] emphasized the ability of these children to tolerate severe emaciation well.

The infant has only a few ways in which to express undue emotional tension. He can refuse food, cry excessively, and vomit. During infancy many of the so-called "feeding problems" may very well be related to a severe emotional disturbance in the mother, which in some unknown way is transferred to the baby. Just exactly how the psychic tension is transmitted to the child is poorly understood. Some babies as early as 2 months of age are capable of responding to their mothers by smiling and later by laughing. The mother soon learns that she can play with the child long before the faculty of language is established. He responds to rattles, games of peekaboo, and other pleasant stimuli in a happy manner. The preverbal communication between the mother and the child is known as empathic communication. If the mother can communicate positive and happy feelings to the baby by the tone of her voice and expression on her face, it would seem reasonable to assume that disturbances in the mother, which produce tenseness and anxiety in her voice, as well as in her behavior, can also be communicated to the child through this emphatic relationship. If no definite organic basis for

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1. English, O. S., and Pearson, G. H. J.: Emotional Problems of Living, New York, W. W. Norton & Company, Inc., 1945, p. 186.

2. Bettelheim, B.: Love is not Enough: The Treatment of Emotionally Disturbed Children, Glencoe, Ill., The Free Press, 1950, pp. 193-196.

3. Kanner, L.: Child Psychiatry, Springfield, Ill., Charles C Thomas Publisher, 1948, p. 393.

the vomiting of a baby can be established, the emotional attitude of his mother should be thoroughly investigated. The two following case reports illustrate the reaction of babies to an emotionally disturbed mother.

CASE 1.—A 6-week-old baby was admitted to the University of Kansas Medical Center Hospital because of vomiting and failure to gain weight. The vomiting had been of such an amount that on admission to the hospital the infant weighed somewhat less than it did at birth and was dehydrated. At no time after admission to the hospital did the baby vomit. The dehydration was corrected, and during a stay of two weeks' duration the baby gained weight and was well above its birth weight at the time of its discharge.

The family history indicated that there were three older siblings. The family had a submarginal income. The father was a severe chronic alcoholic who went on frequent "binges," during which time he was absent from home for periods of several days. The mother attempted to supplement the income by working. Often the family was left financially destitute during the father's absence. At the time of discharge from the hospital, the attending pediatrician stated that he thought the baby would be back in the hospital, if and when the father went on another alcoholic "binge." Two weeks later the baby was again admitted to the hospital because of vomiting for the previous three days. It was ascertained that the father had gone on another "binge" the same day the baby began vomiting. No vomiting occurred during the baby's hospital stay. It began to thrive and again was discharged. Further follow-up study was precluded by the family's departure to another part of the country.

CASE 2.—A 15-month-old white boy baby was admitted to the University of Kansas Medical Center Out-Patient Department with the chief complaint of vomiting for 13 months. This vomiting started when the child was 7 weeks of age and he "vomited frequently" and would act "colicky." His appetite remained good, and he continued to gain weight. At 4 months of age he was given "yellow pills" by a private physician and was much better but continued to vomit two or three times daily. At the time of his admission to the Medical Center he was vomiting two or three times daily. Physical examination, including a gastrointestinal serial study, showed nothing significant.

Investigation of the family relationships indicated that the mother and father of this child were having considerable marital difficulties and that they had already sought help from a psychiatric social worker, who did some marriage counseling with them. Despite this treatment the marital situation was still highly unsatisfactory, and both the husband and the wife had seriously considered divorce. Psychotherapy was started with the mother. The father was seen once by a psychiatrist, but seemed unwilling to participate in further interviews, saying that he was too busy with his farming.

The mother was seen in weekly interviews for a period of about a year, during which time the father and mother separated for a while, and the child lived with his aunt and uncle. Within a few weeks of the beginning of therapy, the child's vomiting decreased. The mother was able to verbalize her irritation with the child and the fact that she became furious with him when he would disturb things around the home. She would frequently lose her temper and yell at him and spank him. The child responded by vomiting, often on her. As the mother began to see the connection between her explosive behavior toward the child and the child's vomiting she became more patient with the child, and in a period of about four weeks the vomiting decreased noticeably. In a period of about three months the vomiting had completely ceased, and a follow-up two years later indicated that he was a healthy well-nourished happy boy, free from any gastrointestinal upset.

It is obvious in such cases that direct treatment of the baby or child is unnecessary. Psychological vomiting in infants is easily diagnosed by the simple expedient of hospitalizing them. Almost universally the vomiting stops with the removal of the baby from the disturbing environment of the home. This observation helps in making a differential diagnosis between organic and psychologic disease.

The treatment of these patients requires that the basic emotional difficulty in the parents be resolved. Any psychotherapy, therefore, is directed towards the parents and not the child. If a successful resolution of the parents' problem is impossible, the child should be placed in a warm friendly environment, so that it need no longer react to the emotional stresses of those who care for him. Children up to the age of about 5 years who have emotional vomitiong will respond satisfactorily to simple environmental manipulation or psychiatric treatment of the parent.

As the child gets into the school age or older, vomiting becomes more difficult to treat, and combined therapy of parent and child is often necessary. Here the symptom of vomiting may appear less directly related to obvious emotional disturbances in the parent. The vomiting often makes its appearance following a traumatic experience to the child, such as an operation or infectious illness. In these cases it would appear at first glance that the operation or illness was the "cause" of the vomiting. This is not so. The operation or infectious illness is only the trigger mechanism setting off the reaction which has been building up for many months or years previously. The basic difficulty is to be found again in the parent-child relationship, and the ultimate cure is brought about by correcting the basic difficulties in the parent-child relationship, as illustrated by the following cases.

Case 3.—A 6-year-old girl was admitted to the University of Kansas Medical Center Hospital with a chief complaint of failure to eat and wasting away for the past week. About three weeks before admission, the child had had chickenpox, from which she recovered uneventfully. She was eating and up and around playing. About one week before admission, she began complaining of a headache and began vomiting her meals. She was admitted to another hospital, where she stayed for two days, and was given fluids intravenously. The doctors in this hospital felt that she was not doing well psychologically, and sent her home, hoping that this would improve her psychological difficulties. However, the child continued to vomit, started to refuse food, and became mute. It was with these symptoms that she was admitted to the University of Kansas Medical Center. Physical examination and laboratory tests showed nothing significant.

When the child was first seen in psychiatric consultation, she refused to talk, seemed to be comatose, and did not respond upon being spoken to. It was possible, however, to attract her attention by playing with the doll in her crib, and finally she would shake her head "yes" or "no" to questions. The comment was made to her that something must be terribly wrong that she had to vomit and refuse food and wouldn't talk. She was asked whether she was worried about something and she shook her head that she was. Further communication with her was impossible. Following this interview, she was spectacularly improved; she sat up, talked, and ate. She was seen in daily play sessions for about three weeks, during which time her vomiting stopped completely, and she ate well. She was returned to her home and seen once weekly in play sessions for a period of approximately six months.

The girl presented the picture of an extremely hostile child who was unable to admit her hostility. In the play sessions she attacked the therapist continually with cork guns and clay and verbally by calling him names and saying that he was "too dumb" to know what she wanted to play with. As the therapy progressed, she modified this behavior by becoming more friendly with the therapist and being willing to play on an occasional give and take basis. For about six weeks she would deny interpretations to the effect that she was angry. However, they were repeatedly made, because her play was hostile, and her facial expression showed considerable anger toward the therapist. One day, she suddenly blurted out, "All right, all right; I do get mad at my mother." From this time on, the hostility toward the therapist almost ceased to exist, but the child directed it toward her mother. For example, following a play

session, she returned to her mother and said, "Come on, Stink, let's go home." In the final phases of therapy, the hostility toward her mother disappeared, and the child became able to relate herself in an adequate manner to her parents.

Work with the mother indicated that the patient was an only child, conceived after a long period of infertility, and born after many hours of difficult labor. Because of these facts, the mother felt that this was the only child she would ever have and overprotected this child and smothered her with care. The child was never allowed to walk to school and was always taken in an automobile to and from school. Her mother felt that she had a great deal of bronchial trouble and kept the child in the house most of the time and out of school frequently. Furthermore, the mother was determined that the child would not have a "bad temper." Her reason for feeling so strongly about this was that the mother had red hair and was teased

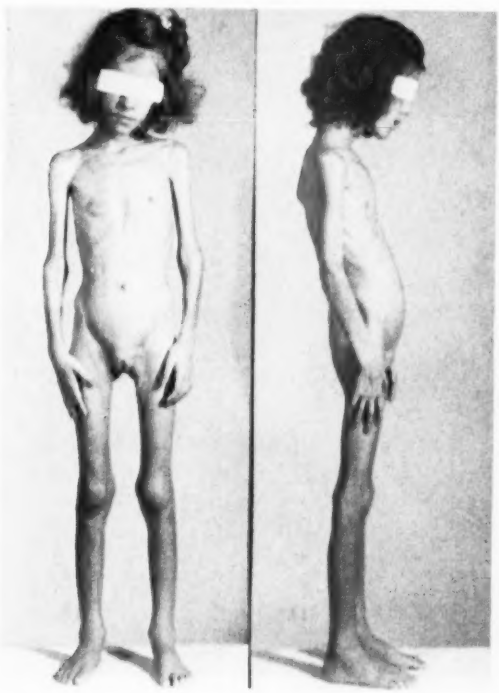

Fig. 1 (Case 4).—The patient as she appeared at the time of her admission to the University of Kansas Medical Center. Note the severe emaciation and stooped posture.

about her temper as a child. When the patient was born, she had red hair. The mother was determined that this child would not show any temper outbursts. The mother described the child as always having "nervous vomiting," and the parent carried a pan in the car for the child to vomit in because she "always gets car sick." Therapy was directed toward getting the mother to treat the girl in a more relaxed and less overprotecting manner. The mother was able to do this, allowing the child to walk to and from school and allowing her considerably more freedom of expression than she had ever had before. As these remedial steps were taken, all of the nervous vomiting and the car sickness disappeared. A two-year follow-up shows the child to be free of vomiting and well adjusted.

Case 4 (Fig. 1.).—A 7-year-old white girl entered the University of Kansas Medical Center Hospital twice. The first time she was treated symptomatically for "nausea of two years' duration with vomiting, irritability, and nervousness." She was extremely emaciated, weighing

27½ lb. (12.4 kg.) with a height of 43¼ in. (109.9 cm.). After some improvement, she was discharged to her home, where she continued to vomit, and was readmitted to the hospital several months later in an extremely emaciated state. It was felt that it would be necessary to hospitalize her again and that her prognosis for life was grave because she was suffering so severely from malnutrition. She did poorly in the hospital for about the first two weeks, curling up in a fetal position, vomiting everything she ate, and frequently refusing food. She almost constantly made peculiar gulping sounds and movements which resembled the gulping movements of a fetus. It was difficult to stimulate her sufficiently to get her into any play sessions. Very early in the course of her stay she was asked why she came to the hospital, and she replied that she was sick. She was asked why she was so sick and she replied, "Worry." It then came out that her father and mother fought all the time and that the child was worried

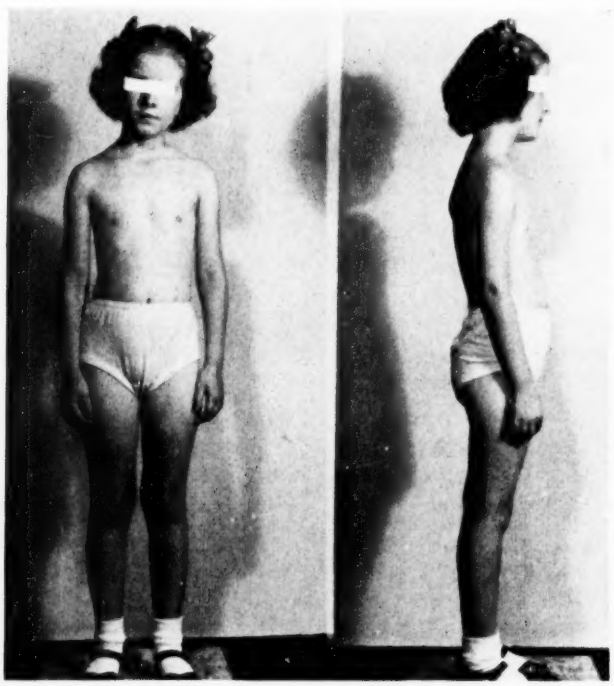

Fig. 2 (Case 4).—The patient as she appeared after two years of treatment in a psychiatric receiving home.

for fear the mother would be hurt or that the father would not come home some evening. She said that she was less worried when she was in the hospital, but that she would like to stop her father from arguing with her mother. She said that she had heard arguments in the night and that her father used "terrible words," many of which she didn't understand. When asked what she would do to stop her father from fighting with her mother, she said she would bite him.

Past history indicated that the child had had a tonsillectomy about a year and a half before her admission. The symptom of pernicious vomiting started following the tonsillectomy. She remained in the hospital about two months and was transferred to a treatment home for a period of about 18 months. During this period of time she changed from a severely withdrawn, fearful, and unexpressive child to a normally out-going, confident, and happy child. Her early sessions were filled with fear of being destroyed. One of her favorite games was to have the therapist be a fox and she was a chicken, the idea being that the fox was supposed

to catch the chicken and eat it up. She used nearly every object in the room as a "safe base," in order to protect herself from the therapist. She also had "king's six," another form of magical safeguarding. She was able to say that she feared having her tonsils out and was angry with her parents for forcing her to have them out. However, she was unable to express any of these feelings to her parents at the time. It became obvious to us that her vomiting was an expression of her hostility toward adults. Whenever she became angry with an adult, she would start to gulp and would vomit. More than once she vomited on the therapist when she was angry with someone in the treatment home. If the therapist succeeded in getting her to verbalize her anger before she vomited, the gulping would stop and there would be a complete change in her personality. She would brighten up and start to play instead of withdrawing, gulping, and eventually vomiting.

Investigation of the parents' difficulties indicated that the father was an alcoholic and an inadequate individual who was unfaithful to his wife, particularly during the times that she was pregnant with the patient and her brother, who was five years older. As a result of her husband's inadequate behavior, the mother became very disappointed with the marriage and turned to her daughter for emotional support. The child was tightly bound to her mother emotionally, and the mother literally carried the child like a sack of feed. It was felt that the mother unconsciously enjoyed having her daughter sick, because then the child could stay home from school and be even more closely tied to her parent. Therapy with the mother and father was directed toward getting him to abandon his alcoholism, which was successful, and helping the mother to see that the patient needed to verbalize her feelings of resentment and to "stand up for herself in a normal way." It was pointed out to the mother that the child could be literally "too good," and thus forced to hold in all of her feelings of anger. The child returned to her home after two years of inpatient treatment and made a good adjustment. She went to school and was able to assert herself. On one occasion, when her father became too demanding of her at the breakfast table, she simply refused to eat with him, saying to her mother, "Daddy yells too much at me at breakfast, so I won't come down to eat until he stops." The mother conveyed this thought to the father, and the father modified his behavior accordingly. A follow-up a year later indicated that the child is free from vomiting and getting along well (Fig. 2).

The symptom of vomiting is often misinterpreted or overlooked, and, yet, if the total picture were more carefully studied, mistakes in diagnosis could be reduced. Such cases are constantly coming to the attention of the child psychiatrist, and, in retrospect, it is appreciated that vomiting has been a persistent and recurring symptom, long before the onset of obsessions, compulsions, or other forms of behavior problems. For example, there is the case of the 13-year-old girl who came to the attention of the psychiatrist because she believed that she had killed an insurance salesman and that her dog had eaten the body. While in the hospital, she looked out the window and saw a piece of paper in the bushes which she misinterpreted as someone's arm which the doctor had cut off and thrown out the window. This child was obviously disturbed in adolescence and either psychotic or on the verge of a psychosis. Yet, this same girl was referred to a psychiatrist at the age of 5 years for repeated and persistent vomiting and was pronounced "normal." Perhaps if more attention had been paid to the symptom at that time and the basic difficulties corrected, such a serious break might have been prevented.

Cobb[4] pointed out that vomiting is one of the most frequent hysterical symptoms in adults. Frequently, the symptom of vomiting is part of the general picture of emotional disturbances in a child, as evidenced by a 16-year-old adolescent girl who lives away from her parents; each time she goes home, this

4. Cobb, S.: Emotions and Clinical Medicine, New York, W. W. Norton & Company, Inc., 1950, pp. 198-200.

girl vomits and breaks out in hives. Her basic difficulty is one of amnesia and hypersomnolence, not vomiting. In cases of this sort the vomiting should be easily recognized as a psychogenic symptom.

Weber [5] reports a case of vomiting in a woman so severe that she was able to vomit feces and enemas. The onset of her illness followed the death of her husband on their wedding night. Reports of this sort are common in the older literature, and their validity may be questioned, but there is little doubt that vomiting of a less spectacular nature is seen frequently in medical and pediatric practice today.

SUMMARY

Vomiting is a common symptom of emotional disturbances in babies, children, adolescents, and adults. It is frequently misinterpreted as pyloric stenosis, pylorospasm, or other organic diseases. Cases illustrating the psychogenic nature of vomiting and specific psychodynamics have been cited.

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FUNCTIONING ADRENAL TUMORS IN CHILDHOOD

Consideration of Diagnosis, Surgical Approach, and Postoperative Management

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THE OCCURRENCE of hormone-producing neoplasms of the adrenal cortex is rare in childhood. Approximately 30 instances of Cushing's syndrome and 55 cases of virilism due to adrenal cortex tumor have been described in children between the ages of 3 months and 10 years.[1] Differential diagnosis may be difficult, and surgery is often hazardous and complicated by postoperative adrenal insuffi-

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ciency.[2] This report deals with a child with Cushing's syndrome and one with adrenal virilism and presents a discussion of some of the problems of diagnosis, surgical approach, and postoperative care.

METHODS

Skeletal age was estimated by comparison of a roentgenogram of the hand and wrist with the standards of Todd [3] or by the 67-ossification-center survey.[4] The 17-ketosteroid excretion was determined by the simultaneous hydrolysis and extraction of urine with toluene [5] and the aqueous alkali colorimetric procedure of Koch.[6] Dehydroisoandrosterone-like compounds were measured by Allen's adaptation [7] of the procedure described by Dirscheri,[8] using the equation derived by Allen [9] to correct for interfering color in urine extracts. Formaldehydogenic corticosteroids were measured by oxidation of a neutral lipid extract made from urine at pH 1.5.[10] The gonadotropin content of urine was measured by bioassay.[11] Urine chloride content was estimated at the bedside by the Fantus test.[12] Other procedures were done by methods in routine use in the

2. (*a*) Kolff and Tjiook.[1j] (*b*) Wilkins.[1k] (*c*) Talbot, Sobel, McArthur, and Crawford.[1o] (*d*) Weinberg, T.: Contralateral Adrenal Atrophy Associated with Cortical Adrenal Neoplasms, N. Y. J. Med. **41**:884, 1941. (*e*) Cahill, G. F.; Melicow, M. M., and Darby, H. H.: Adrenal Cortical Tumors; Types of Nonhormonal and Hormonal Tumors, Surg., Gynec. & Obst. **74**:281, 1942. (*f*) Thompson, K. W., and Eisenhardt, L.: Further Consideration of Cushing's Syndrome, J. Clin. Endocrinol. **3**:445, 1943. (*g*) Spence, H. M., and Thompson, F. G., Jr.: Hormone-Producing Tumor of Adrenal Cortex with Congenital Absence of Contralateral Adrenal Gland: Report of Case, New Eng. J. Med. **236**:13, 1947. (*h*) Goldberg, M. B.; Gordan, G. S.; Deamer, W. C.; Hinman, F., and Rapaport, E.: Cushing's Syndrome from Adrenal Cortical Tumor with Special Reference to Surgical Mortality: A Report of 3 Cases and Review of the Literature, J. Clin. Endocrinol. **10**:839, 1950. (*i*) Thorn, G. W.; Forsham, P. H., and Emerson, K. Jr.: The Diagnosis and Treatment of Adrenal Insufficiency, Publication No. 29, American Lecture Series, Monograph in American Lectures in Endocrinology, edited by W. O. Thompson, Ed. 2, Springfield, Ill., Charles C Thomas, 1951. (*j*) Nichols, F. S.; Root, S. A., Mirabile, C. S., and Lampson, R. S.: Cushing's Syndrome Treated by Removal of Adrenal Cortex Tumor, New Eng. J. Med. **247**:11, 1952.

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12. Fantus, B.: Fluid Postoperatively: Statistical Study, J. A. M. A. **107**:14, 1936.

laboratories of the Children's Hospital. Urine was kept cold during collection and was preserved at —30 C. Most of the collections from Patient 2 were made during 12 hours at night rather than for 24 hours. The 24-hour excretion was calculated from the ratio of the creatinine excreted to the 21 mg. per kilogram of body weight expected.[13] In this way minimal values probably were obtained, as hormone excretion is at the low point of its diurnal variation during the night.[14]

DATA ON PATIENTS

PATIENT 1.—R. H., born Oct. 15, 1941, was admitted to Children's Hospital on April 7, 1950, at 8½ years. He had apparently been perfectly well until 13 months prior to admission, when he

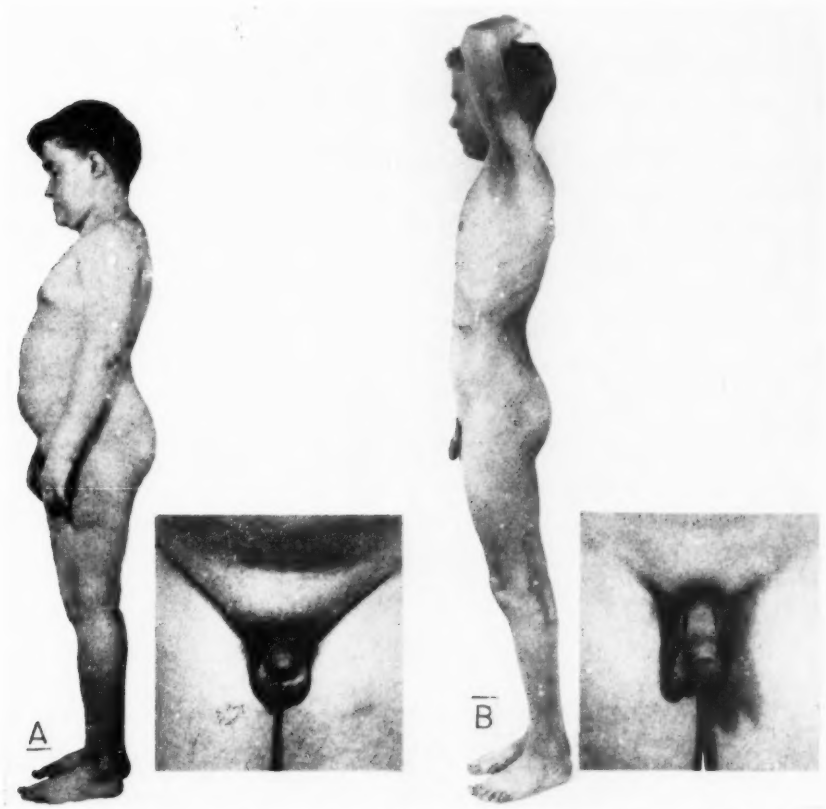

Fig. 1.—*A*, preoperative photograph of Patient 1 at age 8½ years. Generalized obesity is evident, as are the cervical fat pad and rounded face. The insert illustrates the presence of pubic hair and the relatively small testes. *B*, photograph of the same patient one and one-half years after removal of a left adrenal cortex tumor. The body build has returned to normal, and the photograph has been adjusted to represent accurately the increase in height. Genitalia (insert) are those of normal adolescent boy.

13. Clark, L. C., Jr.; Thompson, H. L.; Beck, E. I., and Jacobson, W.: Excretion of Creatine and Creatinine by Children, A. M. A. Am. J. Dis. Child. **81**:774, 1951.

14. Pincus, G.; Romanoff, L. P., and Carlo, J.: A Diurnal Rhythm in the Excretion of Neutral Reducing Lipids by Man and Its Relation to the 17-Ketosteroid Rhythm, J. Clin. Endocrinol. **8**:221, 1948. Romanoff, L. P.; Plager, J., and Pincus, G.: The Determination of Adrenocortical Steroids in Human Urine, Endocrinology **45**:10, 1949.

had an uncomplicated case of chicken pox. Following this his appetite increased, and his weight increased from 52 lb. (23.6 kg.) to 70 lb. (31.8 kg.) in 8 months, and to 92 lb. (41.7 kg.) at the time of admission. There had been no change in the rate of growth in height. Four months before admission pubic and axillary hair appeared, and the penis began to enlarge. For two or three months he had been complaining of moderately severe headaches weekly and had experienced occasional pain in the upper abdomen. There had been no visual disturbance. His face had become quite round. No change in skin color had been noticed, and there was no tendency to bruise. Although his activity had diminished, he had good muscle strength. His appetite was good, and his water intake was generous. There was no polyuria or nocturia. There were no respiratory tract symptoms. There was no family history of endocrine disturbances, but several of the mother's relatives had achieved menarche at an early age (9 to 10 years).

TABLE 1.—*Summary of Physical Findings, in Each of the Patients Here Reported, Before and After Operation*

	Age, Yr.	Height Age, Yr.	Weight Age, Yr.	Bone Age, Yr.	Virilism	Testes Enlarged	Areolar Development	Skin	Blood Pressure
Patient 1									
Preoperative	8 6/12	8 6/12	13	11	Yes	No	Yes	Seborrhea, flush	140/90
Postoperative	9 7/12	11	10 6/12	13	Yes	Yes	No	Normal	108/68
Patient 2									
Preoperative	2	2 4/12	3	4 6/12	Yes	No	No	Seborrhea	86/50
Postoperative	3	3 1/12	3 10/12	5 6/12	No	No	No	Normal	86/52

TABLE 2.—*Summary of the Laboratory Data, in Each of the Patients Here Presented, Before and After Operation*

	HGB., Gm./ 100 Cc.	Eosinophiles/ Cu. Mm.	CO_2, mEq./L.	pH	Chloride, mEq./L.	Glucose Tolerance Test, Mg./100 Cc.	17-Ketosteroids, Mg./24 Hr.	Dhia * Mg./24 Hr.	Corticosteroids, Mg./ 24 Hr.	F.S.H., Mμ/24 Hr.
Patient 1										
Preoperative	15.4	3-14	29.3	7.54	110.8	67; 216; 215; 186; 154	8.0-24.0	Neg.	2.0	Neg. 3.0
Postoperative	13.2	124	....	....	.....	.....	1.9-2.9	.....	0.2	Pos. 26
Patient 2										
Preoperative	12.3	81-220	22.5	7.45	107.6	64; 168; 148; 97; 118	72.0-155.0	28.0-47.0	0.12	Neg. 3.0
Postoperative	13.4	....	....	....	.....	.....	1.2-2.4	Neg.	0.23	.....

* Dehydroisoandrosterone.

Physical examination showed an alert moon-faced child of average height for his age, who displayed generalized obesity and had a definite cervical fat pad (Fig. 1*A*). The eyebrows were bushy, and moderate activity of the sebaceous glands of the nose was noted. The skin was very moist and flushed. There were no striae or ecchymoses. Skin tone and muscle strength were normal. The blood pressure was 140/90. There was moderate engorgement of the vessels of the ocular fundi. Confrontation visual fields were normal. The breasts were obese, without palpable glandular tissue, but the areolae was somewhat enlarged. There was a moderate amount of pubic and axillary hair. The penis was larger than normal for the age. The scrotum was heavily rugated and moderately pigmented. The testes were of normal size for the child's age. The heart, lungs, abdomen, and extremities were normal.

Roentgenograms showed normal mineralization of the skeleton and a normal sella turcica. The bone age was that of a boy 10 3/12 years old. Excretory urograms showed that the left kidney was displaced downward and laterally. Red blood cell count, white blood cell count, and urinalysis were within normal limits. The hemoglobin value was moderately elevated. The total eosinophile count was abnormally low. There was a moderate alkalosis. The carbohydrate tolerance was diminished. The 17-ketosteroid excretion was 8 to 24 mg. per 24 hours (normal,

1 to 5 mg.), and the corticosteroid excretion was 2.0 mg. per 24 hours (normal, 0.2 to 0.7 mg.). The urine was negative for gonadotropin when tested for 3 mouse units per 24 hours. The pertinent findings are summarized in Tables 1 and 2.

The patient was prepared for surgical exploration with 5 ml. of lipoadrenal cortex extract and 20 ml. of aqueous adrenal cortex extract administered intramuscularly on the night before and on the morning of the operation. Just before the exploration an infusion containing 25 ml. of aqueous adrenal cortex extract was started through a catheter in the right saphenous vein. The operation was performed through a transverse upper abdominal incision. The right adrenal gland was exposed and palpated and was thought to be of normal size. No biopsy was done. In the left adrenal an encapsulated spherical tumor measuring 3 cm. by 3.5 cm. by 4 cm. was found and removed without difficulty. The tumor weighed 28.5 gm. (Fig. 2). Microscopic

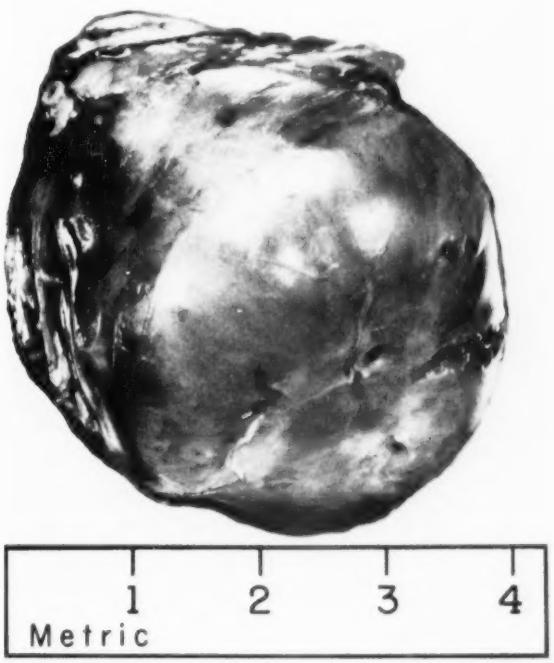

Fig. 2.—Gross appearance of the tumor from Patient 1. It measured 3 cm. by 3.5 cm. by 4 cm. and weighed 28.5 gm.

examination [15] showed that the tumor consisted of cords and nests of polyhedral cells with oval moderately vesicular nuclei and abundant finely vacuolated cytoplasm (Fig. 3*A*). Some of the nuclei were very large and contained prominent nucleoli. There were scattered small groups of irregular multinucleated cells containing two or three densely staining large nuclei and having a prominent basophilic nonvacuolated cytoplasm (Fig. 3*A*). No mitotic figures were seen, and stromal elements were not prominent. Small amounts of Sudanophilic lipid material were demonstrated in the cytoplasm of the tumor cells by Sudan stain. In focal areas the tumor cells were swollen and appeared partially degenerated (Fig. 3*B*). At one edge of the tumor there was a thin rim of compressed and partially atrophic cortex (Fig. 3*B*).

All fluids and blood administered after identification of the tumor contained 10 ml. of aqueous adrenal cortex extract per 100 ml. of fluid. During the first 24 hours a total of 150 ml. of

15. Interpretation of the pathological sections was made by Dr. David Freiman.

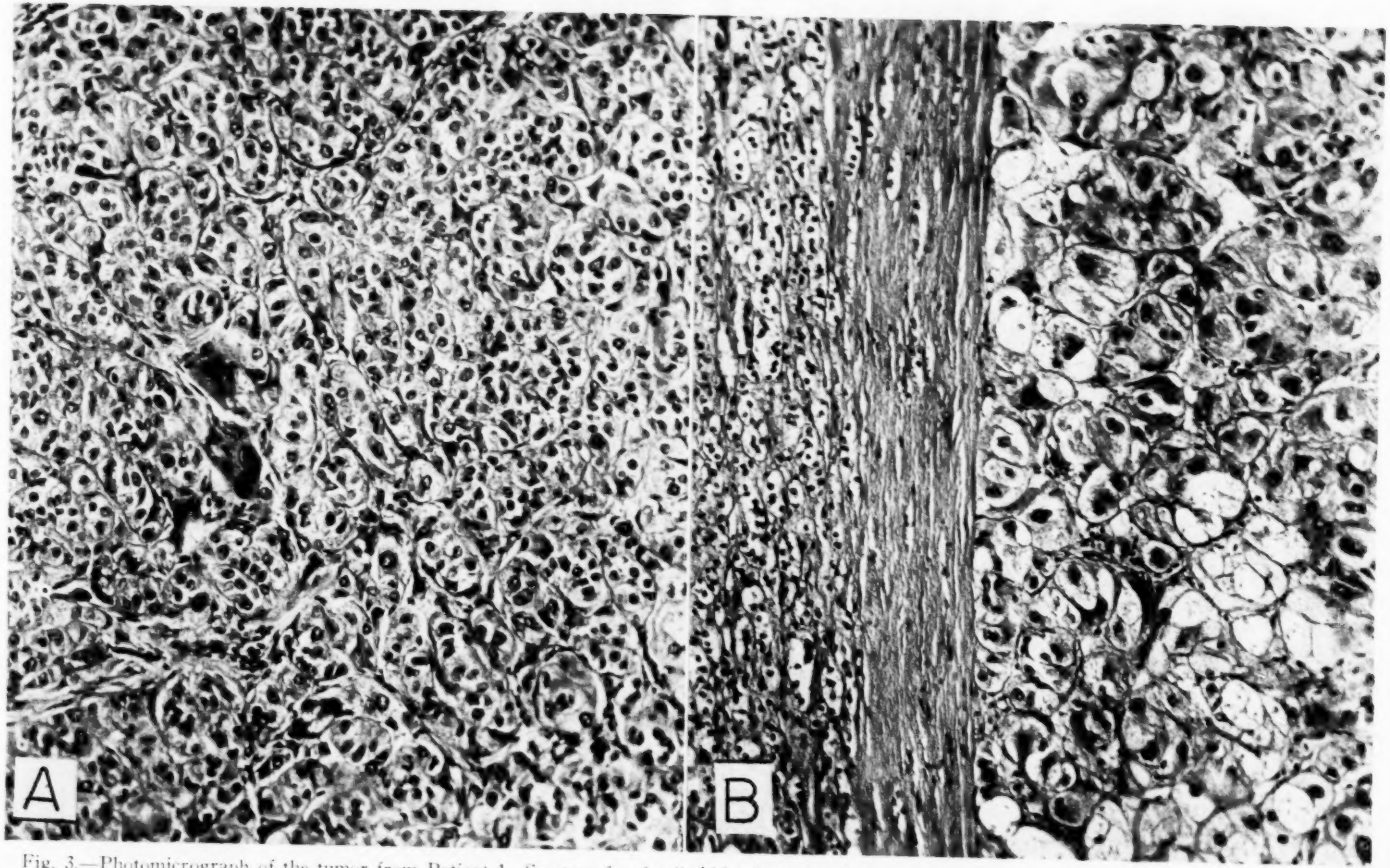

Fig. 3.—Photomicrograph of the tumor from Patient 1. See text for detailed histologic description. In *B*, a thin rim of compressed and slightly atropic but otherwise normal cortex is seen. Hematoxylin and eosin stain; × 160.

aqueous extract was given intravenously. Thereafter the amount used was gradually reduced, 80 ml. being given on the second and third days, and 70 ml. on the fourth day. At this stage the child was able to take liquids by mouth, and the extract was given intramuscularly at four-hour intervals. The dose was reduced and the interval lengthened until treatment was discontinued entirely on the 11th postoperative day. Lipoadrenal extract was used only on the first three days after removal of the tumor in doses of 5 ml. each day. A 2-mg. dose of desoxycorticosterone acetate in oil was given on each of the first two days. Salt balance was maintained by varying the proportions of 5% dextrose in water and 5% dextrose in saline in the infusion. For the first three days after discontinuation of intravenously administered fluids three 1-gm. salt tablets were given daily.

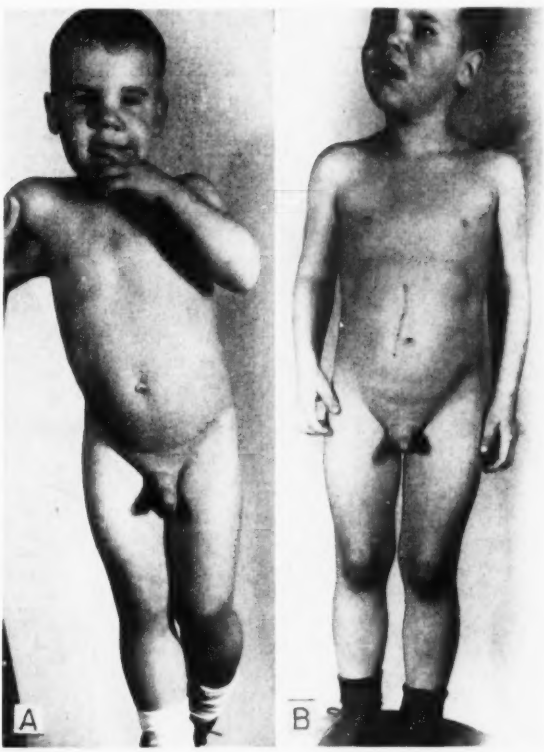

Fig. 4.—*A*, preoperative photograph of Patient *2* at the age of *2* years. The body habitus is that of a sturdy boy rather than that of a baby. A small amount of dark pubic hair was present but does not show well in the photograph. The penis and scrotum show premature development, but the testes are normal in size. *B*, photograph taken one year after removal of a right adrenal cortex tumor and six months after operation for intestinal obstruction (see text). The transverse scar of the first operation is barely visible. The more recent vertical scar remains prominent. The child's growth has been normal, and the genital development has regressed to normal.

The early postoperative course was essentially uneventful. Moderate tachycardia and drowsiness were attributed to the 10% alcohol content of the aqueous extract. The blood pressure and hydration were satisfactory. The serum concentration of nonprotein nitrogen, sodium, and chloride and the carbon-dioxide content remained normal. There was a slight depression of serum potassium. The findings on electrocardiogram remained normal. The wound healed cleanly, and sutures were removed on the seventh and eighth postoperative days. The patient was slow to recover an interest in eating and by the 10th day was vomiting occasionally, was

pale, and complained of headache. The fasting blood sugar was found to be 26 mg. per 100 cc. on the 12th postoperative day. As there was no evidence of adrenal insufficiency, it was believed that the hypoglycemia might result from a continued excessive production of insulin after the tumor, which had provoked hyperglycemia, had been removed. Therefore, no endocrine therapy was given, but a high-protein low-carbohydrate diet was instituted. No further complications occurred, and the patient was discharged 15 days after operation.

He has remained well for the ensuing two and one-half years. One month after removal of the tumor he weighed 81 lb. (36.7 kg.), was not flushed, and the blood pressure and eosinophile count were normal. Four months postoperatively there was no longer any suggestion of Cushing's syndrome, the pubic and axillary hair had diminished considerably, and the scrotal development had receded entirely. During the next few months masculinization reappeared, the testes

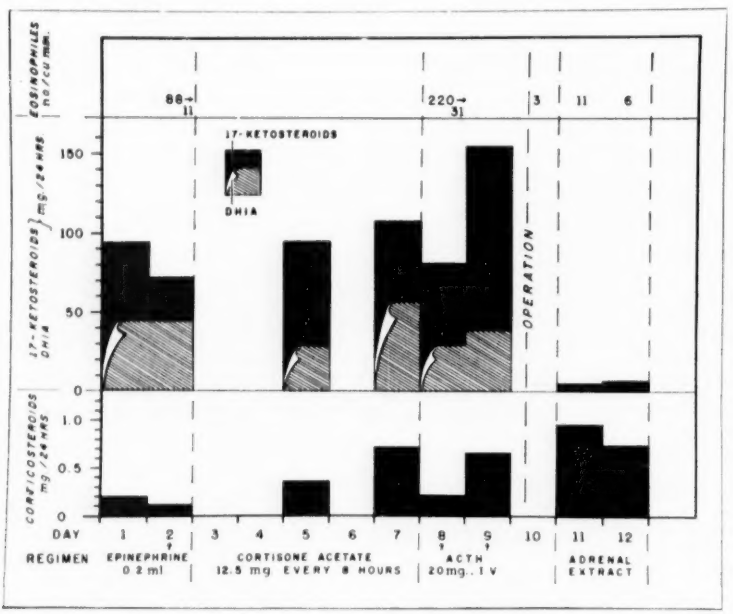

Fig. 5.—Summary of the steroid excretion and the eosinophile count of Patient 2 on the indicated regimes. Corticosteroid and total 17-ketosteroid levels are indicated by the black columns, while the shaded columns represent dehydroisoandrosterone (DHIA). It will be noted that there was no reduction in 17-ketosteroid excretion when cortisone was administered; there was a possible increase in response to corticotropin (ACTH). The augmentation of corticosteroid excretion during treatment with adrenal cortex extract represents metabolites of the administered hormone. The eosinophile count diminished in response to both epinephrine and corticotropin and remained low during the immediate postoperative period.

increased in size, and the rate of growth in height increased. The gonadotropin assay of the urine was positive for 3 mouse units per 24 hours seven months postoperatively. At the same time the 17-ketosteroid excretion was normal (1.3 mg. per 24 hours), as was the corticosteroid excretion (0.2 mg. per 24 hours). Excretory urograms demonstrated the left kidney to be in a more normal position. Adolescence progressed normally, and the child resumed the slender body habitus which had previously been characteristic. At 10½ years he had the height and skeletal maturation of a 13-year-old boy, while his sexual maturation was that of a 15-year-old. There has been no indication of a recurrence or metastasis (Tables 1 and 2, Fig. 1 *B*).

PATIENT 2.—J. A. B., born Sept. 18, 1949, was admitted to Children's Hospital Sept. 24, 1951, at 2 years. When he was one year old his skin became oily and comedones developed. Pubic hair began to appear at about 15 months of age. In the six months before admission hair had appeared on the legs, the penis had enlarged, and he had grown rapidly in height. There was no history of infectious disease, neurological disturbance, or gastrointestinal tract disturbance. There was no family history of endocrine disease, and there had been no exposure to hormone preparations, such as testosterone.

He was a tall sturdy boy who had lost virtually all the habitus of a baby (Fig. 4*A*). The skin was of normal color and texture except for numerous comedones about the nose and chin. The muscles were very well developed. There was no obesity. The ocular fundi, heart, lungs, and abdomen were normal. The blood pressure was 86/50. There was a small amount of coarse pubic hair, the penis was unusually large, and the scrotum was rugated and rather thick. The testes, however, were of normal size for the child's age.

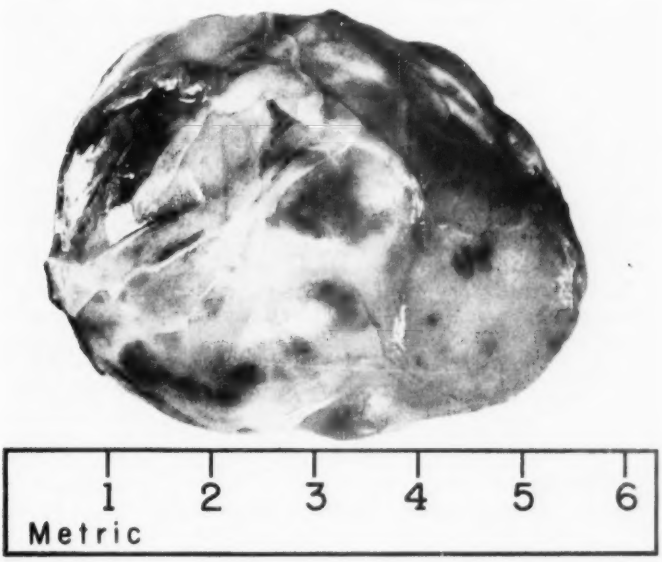

Fig. 6.—Gross appearance of the tumor from Patient 2. It measured 5.25 cm. by 4.5 cm. by 4.5 cm. and weighed 42 gm. It is interesting that this tumor, larger than the one from Patient 1, produced no radiographically demonstrable displacement of the kidney.

Findings on roentgenograms of the skull, chest, and long bones were normal, as were those on excretory urograms. The skeletal maturation was that of a 4½-year-old boy. Red blood cell count, hemoglobin value, white blood cell count, and urine were normal. Total eosinophile count, plasma electrolytes, and carbohydrate metabolism were normal. The assay for gonadotropins was negative for 3 mouse units per 24 hours. The corticosteroid excretion was normal (0.12 mg. per 24 hours). The 17-ketosteroid excretion was 72 to 155 mg. per 24 hours. About one-quarter to one-third of the 17-ketosteroids consisted of dehydroisoandrosterone-like compounds (28 to 47 mg. per 24 hours). A testicular biopsy showed no maturation of either the tubules or the interstitial tissue. These findings are summarized in Tables 1 and 2.

Because of the difficulty in distinguishing between hyperplasia and neoplasia of the adrenal cortex, a short investigation of the effect of corticotropin (ACTH) and of cortisone on the patient's steroid excretion was undertaken in order to collect information which might be of value in future diagnostic efforts. The program and its results are presented in Figure 5. It will be noted that there was a fall in the total eosinophile count in response to both epinephrine

and corticotropin. Cortisone acetate (50 mg. per square meter of body surface by mouth in divided doses for four days) was without influence on the excretion of 17-ketosteroids and dehydroisoandrosterone-like compounds. On the next two days 20 mg. of corticotropin was given intravenously during an eight-hour period. There was no change in the steroid excretion which could clearly be attributed to the corticotropin.

Surgical exploration was undertaken without further hormone preparation. The anesthetic agents were nitrous oxide, ether, and oxygen. A supraumbilical transverse incision was used. On the right a large adrenal tumor was identified and removed without incident. It weighed 42 gm. and was completely encapsulated (Fig. 6). The left adrenal was visualized, and biopsy was done. Although it had seemed of normal size on palpation, gross and microscopic examination of the tissue suggested that all layers of the cortex were atrophic (Fig. 7 *C*). The tumor consisted of masses of large cells with relatively small oval nuclei and abundant finely granular cytoplasm (Fig. 7 *A*) bearing a close morphological resemblance to the cells of the fetal cortex. There were moderate numbers of binucleate cells. Many of the larger nuclei contained one or two prominent and occasionally very large nucleoli. No mitotic figures were seen. There were numerous areas of hemorrhage, a few areas of necrosis, and scattered foci of calcification. Considerable fibrous tissue surrounded and subdivided the tumor, which was evident in isolated islands within the fibrous bands and in the adjacent compressed adrenal gland itself. (Fig. 7 *B*). Except for compression, much of the adjacent gland was intact, and a normal medullary portion was readily distinguished. On another aspect of the tumor, however, a much-thinned atrophic zone of cortex, lying outside a thick area of partially calcified fibrous tissue, was the only remnant of the adrenal cortex.[15] The patient's blood pressure, which had been consistently normal, was 110/60 on the morning of the operation. As anesthesia was induced the blood pressure rose abruptly to 170/120 and remained elevated until one-half hour after surgery was completed. It then dropped abruptly to 100/52 and remained stable at about that level.

When the tumor was recognized, aqueous adrenal cortex extract was added to the infusion which was being administered through a cannula in the saphenous vein. The fluids consisted of 5% dextrose in water or in normal saline, the relative amount of each depending on the clinical status of the patient and on the calculated chloride balance. The estimated salt requirement was 6 gm. per day, about twice the amount ordinarily used for parenteral maintenance of a child the size of the patient.[16] Urine was collected by means of a Foley catheter and analyzed at six-hour intervals. The chloride content was estimated by the Fantus test.[12] The chloride and water excreted were subtracted from the chloride and water intake for the same six-hour period. The rate of the infusion and its saline content were adjusted so as to maintain moderately positive balances of both substances. The child received a total of 95 mg. of aqueous adrenal cortex extract intravenously and 7.5 ml. of lipoadrenal extract intramuscularly on the day of operation. On the second and third days 70 ml. of aqueous extract and 4 ml. of lipoextract were given. The doses were then progressively diminished. Administration of lipoadrenal extract was discontinued on the 5th day and aqueous extract on the 11th day. After the fourth day parenteral fluids were no longer needed, and the adrenal cortex extract was given intramuscularly, the intervals being lengthened gradually from 4 to 12 hours. Two grams of sodium chloride were given by mouth from the fourth to sixth days. The postoperative course was uneventful under this supportive program. The plasma electrolytes were consistently normal. There was no hypoglycemia. The wound healed cleanly, and the child was discharged 13 days after the tumor had been removed.

The 17-ketosteroid excretion had fallen to 7 mg. on the day after operation, and the color test for dehydroisoandrosterone was negative. Urine collections were made monthly, and they continued to show normal amounts of 17-ketosteroids (1.2 to 3.5 mg. per 24 hours) and negative color tests. The skin began to clear immediately. Pubic hair continued to grow rapidly for two months after the operation. Then it diminished in quantity and was no longer present after 10 months. The development of the scrotum and penis receded gradually, so that the genitalia were juvenile when the child was 2 8/12 years old. In May, 1952, six months after operation, he was readmitted to the Children's Hospital with acute mechanical obstruction of the jejunum. At exploration a single "fiddle string" adhesion was found, which had completely obstructed the jejunum. The adhesion was divided, and recovery was uneventful. There was no rise in blood pressure during anesthesia and no evidence of adrenal insufficiency. The anesthetic was

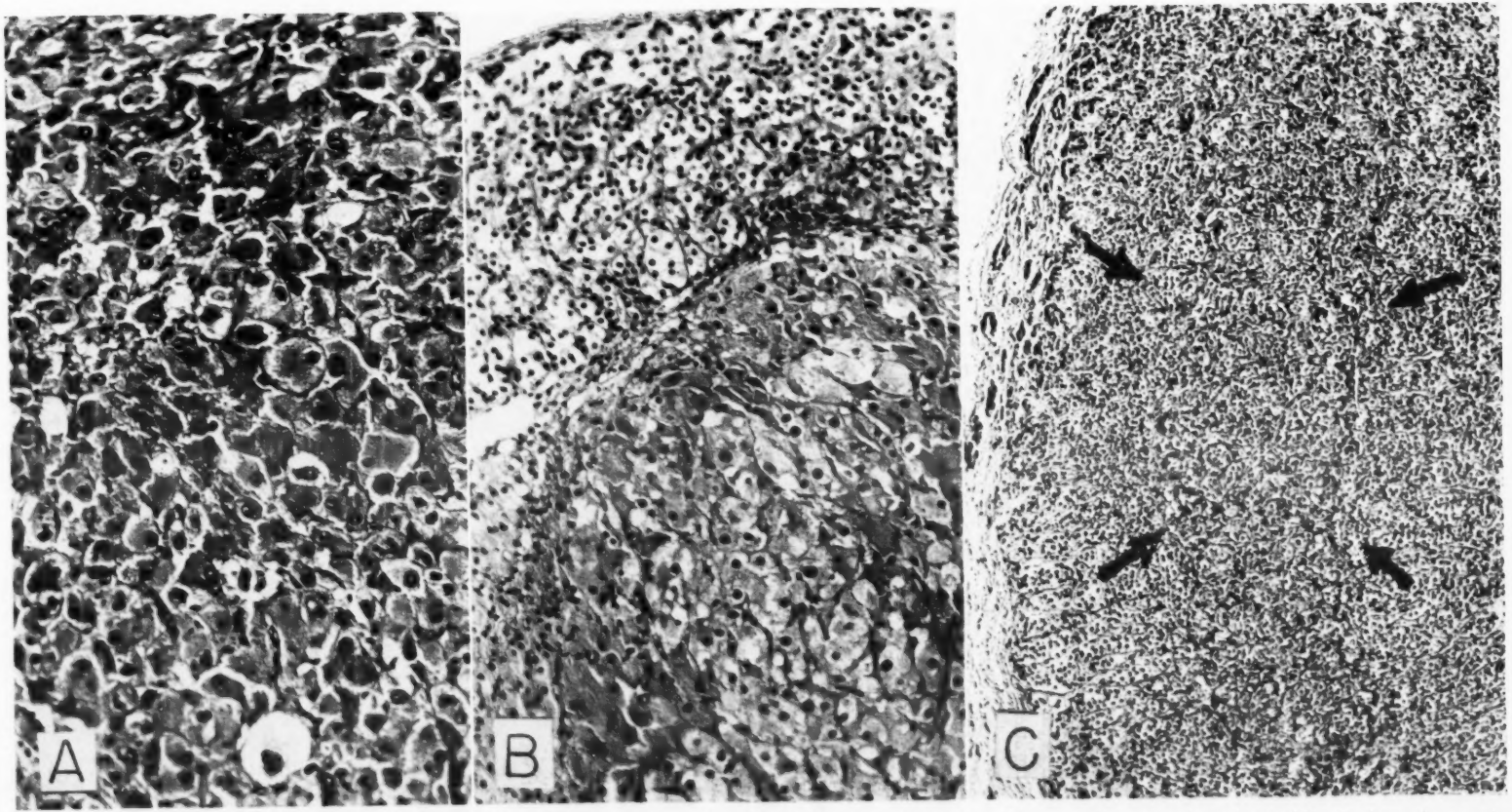

Fig. 7.—*A* and *B*, photomicrographs of the tumor from Patient 2. See text for detailed histologic description. Hematoxylin and eosin stain; × 160. *C*, photomicrograph of biopsy of the nontumorous adrenal gland. The arrows indicate the borders between medulla and cortex. Hematoxylin and eosin stain; × 50.

the same as that used when the adrenalectomy was performed. The child has remained well, and at present, more than one year after removal of the adrenal tumor, there is no indication of a recurrence (Fig. 4*B*).

COMMENT

Diagnostic Considerations.—Patient 1 presented clinical and laboratory evidence of overactivity of all the functions of the adrenal cortex in that he was virilized, obese, hypertensive, and had impaired carbohydrate tolerance. The high 17-ketosteroid and corticosteroid excretion supported the diagnosis chemically. The absence of dehydroisoandrosterone-like compounds in the urine may have been an artifact, as the test was performed on urine which had been frozen for more than a year.[16] Certain features of full-blown Cushing's syndrome were not manifest: The child did not demonstrate weakness, osteoporosis, striae, or the hypochloremic alkalosis which may develop in severely depleted patients.[17] Some children in whom the clinical signs are as evident as in the patient presented may have few chemical abnormalities. In some instances the carbohydrate metabolism has been normal, and the urinary steroids excreted may not exceed normal values.[18] Most children with Cushing's syndrome who are less than 10 years old have an adrenal cortex tumor, but there are reports of bilateral adrenal hyperplasia in children 15 months,[19] 3 years,[20] and 8 years [21] of age. The displacement of the left kidney demonstrated roentgenographically in Patient 1 was of assistance in establishing the probable location of a neoplasm.

The diagnostic problem presented by Patient 2 was more complex. There was evidence of abnormal production of androgens, without suggestion of an increase in the production of hormones regulating carbohydrate or electrolyte metabolism. The masculine development could have resulted from androgens produced either by the adrenal cortex or by the testis. As there was no evidence of an interstitial cell tumor of the testis, the differential diagnosis lay between pseudoprecocious puberty (adrenal cortex virilism) and true precocious puberty with premature activation

16. Gardner and Migeon.[1m] Gardner, L. I., and Migeon, C. J.: Le Diagnostic des Tumeurs Virilisantes du Cortex Surrenalien, Helvet. paediat. acta. **6**:465, 1951.

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18. Wilkins.[1k] Allen, Hayward, and Pinto.[7]

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21. Chute, A. L.; Robinson, G. C., and Donahue, M. A.: Cushing's Syndrome in Children, J. Pediat. **34**:20, 1949.

of testicular function. The testes may be disproportionately small and the assay of the urine negative for gonadotropins in children in whom true precocity is incomplete. In such patients histological examination of the testis may demonstrate development of the interstitial tissue with varying stages of tubular maturation, while in pseudoprecocious puberty the interstitial cells are not developed.[22] The negative gonadotropin assay and the small testes of Patient 2 did not suffice to establish the adrenals as the source of the abnormal hormone. The lack of development of either the interstitial cells or the testicular tubules, as shown by the testicular biopsy, exonerated the testes as the source of androgen. The high 17-ketosteroid excretion further indicated the adrenals as the possible source. The excretion of substantial amounts of dehydroisoandrosterone-like compounds suggested that an adrenal tumor might be present. There have been many reports of positive tests for these substances in the urine of patients with adrenal tumors.[23] However, the color test has been positive in a child with congenital adrenal hyperplasia [7] and has been negative in instances of adrenal tumor.[24] Recently Kelley and Ely [25] have demonstrated that patients with adrenal hyperplasia have high plasma levels of corticotropin, which can be reduced to normal by cortisone therapy. The response of the 17-ketosteroid excretion to cortisone treatment may be of assistance in differentiating between tumor and hyperplasia of the adrenal cortex. That the administration of cortisone will suppress the elevated 17-ketosteroid excretion of individuals with adrenal hyperplasia has been well documented.[26] There are several reports of failure of the ketosteroid excretion to diminish in response to cortisone in patients with adrenal tumor,[27] although in a few instances there had been some diminution of 17-keto-

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26. (*a*) Gardner and Migeon.[1m] (*b*) Jailer, Louchart, and Cahill.[24b] (*c*) Wilkins, L.; Lewis, R. A.; Klein, R., and Rosemberg, E.: The Suppression of Androgen Secretion by Cortisone in a Case of Congenital Adrenal Hyperplasia: Preliminary Report, Bull. Johns Hopkins Hosp. **86**:249, 1950. (*d*) Bartter, F. C.; Albright, F.; Forbes, A. P.; Leaf, A.; Dempsey, E., and Carroll, E.: The Effects of Adrenocorticotropic Hormone and Cortisone in the Adrenogenital Syndrome Associated with Congenital Adrenal Hyperplasia: An Attempt to Explain and Correct Its Disordered Hormonal Pattern, J. Clin. Invest. **30**:237, 1951. (*e*) Wilkins, L.; Crigler, J. F., Jr.; Silverman, S. H.; Gardner, L. I., and Migeon, C. J.: Further Studies on the Treatment of Congenital Adrenal Hyperplasia with Cortisone: II. The Effects of Cortisone on Sexual and Somatic Development, with An Hypothesis Concerning the Mechanism of Feminization, J. Clin. Endocrinol. **12**:277, 1952. (*f*) Shepard, T. H., II, and Clausen, S. W.: Case of Adrenogenital Syndrome with Hypertension Treated with Cortisone, Pediatrics **8**:805, 1951. (*g*) Kelley, V. C.; Ely, R. S., and Raile, R. B.: Metabolic Studies in Patients with Congenital Adrenal Hyperplasia: Effects of Cortisone Therapy, J. Clin. Endocrinol. **12**:1140, 1952.

27. (*a*) Gardner and Migeon.[1m] (*b*) Jailer, Louchart, and Cahill.[24b] (*c*) Venning, E. H.; Pattee, C. J.; McCall, F., and Browne, J. S. L.: Effect of Cortisone on the Excretion of 17-Ketosteroids in Adrenal Tumor, J. Clin. Endocrinol. **12**:1409, 1952.

steroid output in patients later proved to harbor an adrenal neoplasm.[28] The results of cortisone treatment in our patient (Fig. 5) tended to support the suspicion of an adrenal tumor. Although the onset of virilism during infancy may be due to adrenal hyperplasia, the age of the patient at the time masculinization became evident did not assist in establishing the diagnosis, since some children with congenital adrenal hyperplasia do not show signs of virilism until 1 or 2 years of age,[29] while others in whom there is an adrenal tumor may have symptoms at an earlier age than did our patient.[30]

Preparation for Surgery.—In the case of Patient 1 the preoperative diagnosis of adrenal cortex tumor was made with considerable confidence. Since lipoadrenal cortex extract does not become effective for 6 to 8 hours,[31] it was given 12 hours before the scheduled operation as well as on the day of surgery. The intention was to assure an adequate supply of this extract at the time the tumor was to be removed. It is rich in the amorphous fraction and potent in preserving the lives of adrenalectomized animals subjected to stress.

Surgical exploration of Patient 2 was undertaken immediately upon the completion of corticotropin treatment, because it is not known whether corticotropin might provoke more rapid growth of a neoplasm. It was considered as likely that the child had congenital adrenal hyperplasia, as that he had an adrenal tumor, and therefore no further preoperative hormone treatment was given.

The incidence of serious or fatal collapse subsequent to adrenal surgery is so high[32] that 100 ml. of aqueous adrenal cortex extract and 1,000 ml. of blood were on hand in the operating room. Since peripheral vascular collapse may render the initiation of an infusion extremely difficult, a polyethylene catheter was placed in the saphenous vein of each child and was kept open by a slow infusion of 5% dextrose-saline.

Surgical Considerations.—It is of considerable advantage to the surgeon to know the probable location of a suspected tumor. When a large adrenal tumor is present, or when the lesion is calcified, its shadow may be demonstrated radiographically. Urography, either intravenous or retrograde, may be very helpful (Patient 1) or of no value whatever (Patient 2). Displacement of the kidney may be without relation to the size of the tumor (26 gm. in Patient 1, 42 gm. in Patient 2) but large tumors are more likely to have this effect. Although perirenal air insufflation is still used with satisfaction in some clinics, we have abandoned its use because the results are inconsistent and because there is an appreciable risk of air embolism. At the time these two patients were under study we had not yet had experience with the technique of presacral perirenal pneumography recently described by Ruiz Rivas of Spain[33] and Blackwood of Australia.[34] We have since used it in two patients

28. Footnotes 1*m* and 27*c*.

29. Footnote 1*k* and *o*.

30. Footnote 1*d*, *e*, *g*, *h*, *l*, and *n*.

31. (*a*) Thorn, Forsham, and Emerson.[21] (*b*) Thorn, G. W.; Jenkins, D.; Laidlaw, J. C.; Goetz, F. C.; Dingman, J. F.; Arons, W. L.; Streeten, D. H. P., and McKracken, B. H.: Pharmacologic Aspects of Adrenocortical Steroids and ACTH in Man, New England J. Med. **248**:232, 1953.

32. Footnotes 1*k* and *o* and 2*d*, *e*, *f*, and *j*.

33. Ruiz Rivas, M.: Roentgenological Diagnosis: Generalized Subserous Emphysema Through a Single Puncture, Am. J. Roentgenol. **64**:723, 1950.

34. Blackwood, J.: Presacral Perirenal Pneumography, Brit. J. Surg. **39**:111, 1951.

without complication. Evans, who has had extensive experience with abdominal aortography, does not employ it in children, because in young subjects the small size of the aorta and its more medial position in relation to the spinal column make the placement of the needle difficult and dangerous.[35] We have not undertaken aortography in patients under 15 years of age.

The surgical anatomy of the adrenal glands is quite complex. The subject has recently been reviewed in detail by Hollinshead.[36] There is no general agreement regarding the best surgical approach to an adrenal tumor. The problems of precise localization and of determining whether a tumor is present anywhere make the choice of a surgical approach difficult. The occasional anomaly of congenital absence of an adrenal[37] suggests the desirability of locating both adrenal glands before undertaking the removal of one of them. In one of his early papers Cahill mentioned the use of preliminary laparotomy, with palpation of the adrenals as its only objective.[38] If a tumor was demonstrated, the laparotomy wound was closed, and when the patient had recovered sufficiently a transthoracic approach was employed for removal of the tumor. Some surgeons express a preference for a modified kidney incision or a vertical lumbodorsal approach.[41] Either of these offers a good exposure and may be useful when the tumor has been located preoperatively. If attempted localization has been unsuccessful, two incisions may be required, and even then there is no opportunity to search for Marchand bodies or to inspect the ovaries. In two of our patients, not reported on here, detailed study failed to afford a definitive explanation of pronounced virilism in young women. Exploration of the ovaries and the adrenals was done through a transverse abdominal incision. Both patients proved to represent the Stein-Levinthal syndrome: the "large pale ovary" or "oyster ovary."[39] Whether an abdominal incision is to be vertical[40] or transverse[41] is a matter of personal preference. In our experience a transverse abdominal incision just above the umbilicus and with a slight cephalad convexity has afforded a satisfactory exposure of both adrenals and an opportunity to search for other abnormal conditions.

Little mention has been found in the literature regarding the use of procaine infiltration around the adrenal gland immediately prior to removal of the tumor.

35. Evans, A. T.: Personal communication to the authors.

36. Hollinshead, W. H.: Anatomy of the Endocrine Glands, Surg. Clin. North America **32**:1115, 1952.

37. (*a*) Taylor and Wiseman.[18] (*b*) Spence and Thompson.[28] (*c*) Feinblatt, H. M.: Carcinoma of Cortex of Suprarenal Gland with Virilism: Necropsy, Arch. Int. Med. **38**:469, 1926. (*d*) Lukens, F. D. W.; Flippen, H. F., and Thigpen, F. M.: Adrenal Cortical Adenoma with Absence of Opposite Adrenal: Report of a Case with Operation and Autopsy, Am. J. M. Sc. **193**:812 1937.

38. Cahill, G. F.; Loeb, R. F.; Kurzrok, R.; Stout, A. P., and Smith, F. M., Adrenal Cortical Tumors, Surg., Gynec. & Obst. **62**:287, 1936.

39. Stein, I. F., and Leventhal, M. L.: Amenorrhea Associated with Bilateral Polycystic Ovaries, Am. J. Obst. & Gynec. **29**:181, 1935.

40. State, D.: Surgery of Tumors and Hyperfunctioning States of the Adrenal Glands, Surgery **32**:134, 1952.

41. Ellis, F. H.; Dawe, C. J., and Clagett, O. T.: Cysts of the Adrenal Glands, Ann. Surg. **136**:217, 1952.

Kleinberg, Remington, Drill, and Swingle [42] demonstrated that the circulatory collapse which often immediately follows adrenalectomy could be prevented, in dogs, by periadrenal infiltration with 4 to 5 ml. of 4% procaine. The rationale of this maneuver is the blocking of traumatic stimuli through the celiac ganglia. In both of the patients here reported 2% procaine infiltration was employed, and no vasomotor depression occurred in either case. The value of this procedure is not proved, but it is easy to do and may offer added protection.

Postoperative Care.—An excess of adrenal cortex hormones, such as are produced by a tumor, may lead to atrophy of the contralateral adrenal cortex by suppressing the production of pituitary corticotropin.[29] When the tumor is removed, there may be a period of temporary adrenal insufficiency during which fatal collapse may occur. This is most likely to happen in Cushing's syndrome.[43] In some instances a virilizing tumor does not suppress the function of the nontumorous gland,[44] but there have been reports of atrophy of the remaining adrenal gland and of death in adenal insufficiency following removal of a virilizing tumor.[45] In Patient 2 the decrease in circulating eosinophiles in response to epinephrine and to corticotropin (Fig. 5) suggested that some normal functioning adrenal cortex tissue was present.[21] The increase in 17-ketosteroid and corticosteroid excretion on the second day of corticotropin treatment may have been in response to the drug, and the fact that there was no concomitant increase in dehydroisoandrosterone excretion could suggest a response of nontumorous tissue to the corticotropin. The number of determinations is too small to warrant an interpretation. Nevertheless, the biopsy of the patient's left adrenal gland suggested some atrophy of all layers of the cortex. The dose of cortisone used in the test period was not considered sufficient to have diminished the size of a normal gland to this degree. The two days of stimulation with corticotropin did not restore the gland to normal size, although its function may have been reestablished.

Hormone Therapy.—Both of our patients were treated as if they were temporarily lacking in adrenal function. At the time, preparations of cortisone and hydrocortisone for intravenous use were not yet available. Cortisone is absorbed so slowly from intramuscular sites that it cannot be relied on to meet changing hormone requirements. We have preferred not to anticipate prompt response of an atrophic adrenal to corticotropin and have therefore used aqueous adrenal cortex extract as the main hormonal agent. Various methods of measuring the hormone production of animals subjected to stress indicate that the adrenal glands produce the equivalent of 130 to more than 240 ml. of aqueous adrenal cortex extract per square meter of body surface per 24 hours.[46] The latter figure, which is equivalent to about 3 ml. per pound (0.5 kg.) of body weight, was used to calculate approxi-

42. Kleinberg, W.; Remington, J. W.; Drill, V. A., and Swingle, W. W.: The Nervous Factor in the Circulatory Failure Induced in Adrenalectomized Dogs by Intestinal Stripping and a Single Stage Bilateral Adrenalectomy, Am. J. Physiol. **137**:362, 1942.

43. Footnotes 1*j* and 2*d*, *e*, *f*, and *h*.

44. Footnote 1*a*, *c*, and *m*.

45. Footnote 1*c* and *g*.

46. Ingle, D. J.: Optimal Requirements for Adrenal Cortical Hormones as Observed in Adrenalectomized Animals: Brief Review, J. Clin. Endocrinol. **4**:208, 1944. Vogt, M.: The Output of Cortical Hormone by the Mammalian Suprarenal, J. Physiol. **102**:341, 1943.

mate hormone requirements. The patient's pulse rate, blood pressure, and state of consciousness and hydration served as guides to the amount of hormone needed.[47] A rise in pulse rate and temperature, a fall in blood pressure, the development of dehydration, or lack of alertness were considered indication of a need for more hormone and more water. Aqueous extract, when given intravenously, is effective for about two hours; when given intramuscularly or subcutaneously the duration of action is four to six hours.[31] In the first days after operation, aqueous extract was added to the intravenous fluids so that a constant supply was available. After the third day, when the most severe stress was over, the hormone was given intramuscularly in diminishing doses and at lengthening intervals in order to allow the remaining gland to resume its activity without risking a period of adrenal insufficiency.

Lipoadrenal cortex extract is absorbed slowly, becomes effective in 6 to 8 hours, and remains active for about 12 hours.[31] It was used during the period of most severe stress to assure a steady supply of hormones. Desoxycorticosterone acetate was used only in Patient 1. As its action is to promote the retention of sodium and water, and since it may cause excessive potassium excretion, it may be wiser to supply the needed sodium and water by infusion.

Fluid Therapy.—The estimation of water requirement was based on the patient's weight, while sodium was given in accord with calculated estimated needs of patients with adrenal insufficiency.[10] All fluids used contained 5% dextrose in order to avoid episodes of hypoglycemia. The Fantus test for urine chloride served as a basis for rapid calculation of chloride balance. Although the test is not consistently accurate,[48] it may be of value under these circumstances, as failure to excrete 20 to 50 mEq. per liter may indicate that the sodium chloride intake is inadequate, while the excretion of larger amounts may indicate an inadequate supply of hormone.[49]

Sedation.—Because patients with adrenal insufficiency are overresponsive to morphine and barbiturates, approximately two-thirds of the dose usually given to children the size of these patients was administered as needed for pain or restlessness.

Complications.—In both of the patients tachycardia and drowsiness developed during the first two days after operation in the absence of evidence of adrenal insufficiency. These signs were attributed to the fact that aqueous adrenal cortex extract contains 10% alcohol.[31]

Although the blood sugar of Patient 1 was only 26 mg. per 100 cc. on the 12th postoperative day, the only clinical evidence of hypoglycemia was the child's pallor and occasional vomiting. There was no evidence of adrenal insufficiency at this time, and the absence of convulsions when the blood sugar was so low was evidence against adrenal insufficiency.[17f] The explanation of the hypoglycemia may lie in an overproduction of insulin in response to an excess of adrenal cortex hormones of

47. Footnotes 1*k* and *o*, 2*i*, and 31*b*.

48. Taylor, W. H.: Use and Interpretation of the Fantus Estimation of Urinary Chloride, Brit. M. J. **2**:1125, 1951.

49. Marriot, H. L.: Water and Salt Depletion (Croonian Lectures), Brit. M. J. **1**:285, 1947; Fantus Estimation of Urinary Chloride, ibid. **2**:1284, 1951.

the type which promote hyperglycemia. That hyperglycemia induces insulin production has been demonstrated by in vitro studies,[50] and hyperplasia of the islets of Langerhans has been observed in patients who have died of Cushing's syndrome.[51] If pancreatic overactivity should persist for a time after removal of the source of excess adrenal hormones, hypoglycemia might occur and might in part account for the depression, anorexia, and listlessness which commonly complicate the late postoperative course of patients who have been subjected to surgical cure of Cushing's syndrome.

It is of interest that the hypertension which occurred when Patient 2 was anesthetized did not recur during his subsequent operation for intestinal obstruction. The same anesthetic agents were used in each instance.

Follow-up.—Both our patients have made gratifying recoveries. The reappearance of secondary sexual characteristics in Patient 1 was a temporary source of concern. It soon became evident that he was undergoing adolescent development at the unusually early age of 9 years; his growth curve followed an adolescent pattern, his testes enlarged, and his urine contained gonadotropic hormones. The early onset of puberty may have reflected the early menarcheal age characteristic of his mother's family or may have indicated that he had reached the correct physiological age for his puberty [26e] under the influence of the abnormal hormones produced by his adrenal tumor.

It is of interest that in Patient 2 the skin and genitalia began to return to normal as soon as the source of masculinizing hormone had been removed. Nevertheless, the pubic hair, which had been shaved for the operation, continued to grow and did not diminish in amount for several months. A persistent effect on skeletal maturation was also evident since the bone age continued to advance in the year after operation. A similar effect may be seen in children treated with methyltestosterone, in whom the bone age may continue to increase rapidly for a time after administration of the drug has been discontinued.[52]

SUMMARY

Two boys with adrenal tumors are described. In one who had Cushing's syndrome, the diagnosis and localization of the tumor were readily accomplished. In the other the diagnosis of pseudoprecocious puberty rather than true precocious puberty was established by the presence of small testes which were histologically immature, by the absence of gonadotropins in the urine, and by a high 17-ketosteroid excretion. The presence of a tumor was suggested by the excretion of large amounts of dehydroisoandrosterone-like compounds and by failure of cortisone acetate to suppress the 17-ketosteroid excretion; the differentiation from hyperplasia was made

50. Anderson, E., and Long, J. A.: The Hormonal Influences on the Secretion of Insulin, Recent Progr. Hormone Res. **2**:209, 1948.

51. Footnotes 1*b*, 17*h*, and 37*d*. Freyberg, R. H.; Barker, P. S.; Newburgh, L. H., and Coller, F. A.: Pituitary Basophilism (Cushing's Syndrome): Report of a Verified Case, with a Discussion of the Differential Diagnosis and Treatment, Arch. Int. Med. **58**:187, 1936. Weisse, K.: Ein Cushing-Syndrome bei einem 20 Monate alten Mädchen, Ztschr. Kinderh. **65**:9, 1947.

52. Sobel, E. H.; Raymond, C. S.; Quinn, K. V., and Talbot, N. B.: Relative Effect of Methyl Testosterone on Rates of Growth and Rates of Skeletal Maturation of Physically Retarded Children, to be published.

by surgical exploration. Histological examination of the nontumorous gland of the virilized patient demonstrated atrophy of the cortex, although there had been a fall in the number of eosinophiles in response to epinephrine and to corticotropin and a possible increase in 17-ketosteroid excretion in response to corticotropin. Removal of the tumors was accomplished by means of transverse abdominal incisions. Adrenal cortex hormones were used liberally to avoid postoperative adrenal insufficiency. Sodium chloride, dextrose, and water were provided by infusion. The postoperative course of the patient with Cushing's syndrome was marked by hypoglycemia. This patient underwent an early spontaneous adolescence six months after removal of the tumor. Both patients are well, without evidence of recurrence, three years and eighteen months, respectively, after surgery.

METABOLISM OF CREATINE AND GUANIDOACETIC ACID IN PREMATURE AND FULL-TERM INFANTS

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PREMATURE infants excrete much less creatine in the urine than young full-term infants, whose urinary creatine may amount to approximately 40% of the total creatinine.[1]

The present investigation was planned to clarify some of the mechanisms accounting for this difference. Studies were made on the effect of feeding creatine or its precursors on the excretion of creatine, creatinine, and guanidoacetic acid by these infants. In other observations, blood levels of creatine and creatinine were determined in relation to urinary excretion. Analyses were also made of the creatine content of muscle at various stages of fetal development. The results suggest that the premature infant stores or utilizes creatine to a greater extent than does the full-term infant.

METHODS

Observations were made on boy babies who were given partially skimmed cow's milk-carbohydrate feeding mixtures of approximately 110 to 130 calories per kilogram of body weight per day with added vitamins A, C, and D. The nitrogen intakes are indicated in the text. Twenty-four-hour collections of urine were obtained by the procedure of Hoag.[2]

Urinary creatine and creatinine were determined by the procedure of Peters.[3] In several observations (indicated in the text), the enzymatic method of Miller and Dubos[4] was used. Total nitrogen was determined by the digestion of the sample with a mixture of potassium sulfate and sulfuric acid, followed by nesslerization.

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1. (*a*) Paffrath, H., and Ohm, W.: Zur Frage der Kreatinurie des Frühgeborenen, Ztschr. Kinderh. **54**:377, 1933. (*b*) Marples, E., and Levine, S. Z.: Creatinuria in Infancy and Childhood: I. Normal Variations; Creatine Tolerance Tests and the Effect of Amino-Acetic Acid in Normal Infants, Am. J. Dis. Child. **51**:30, 1936. (*c*) Marples, E.: Creatinuria in Infancy and in Childhood: II. Creatinuria of Premature Infants, Am. J. Dis. Child. **64**:996, 1942.

2. Hoag, L. A.: Apparatus for the Quantitative Collection of Urine and of Stools in Male Infants, Am. J. Dis. Child. **44**:770, 1932.

3. Peters, J. H.: Determination of Creatinine and Creatine in Blood and Urine with the Photoelectric Colorimeter, J. Biol. Chem. **146**:179, 1942.

4. Miller, B. F., and Dubos, R.: Determination by a Specific, Enzymatic Method of the Creatinine Content of Blood and Urine from Normal and Nephritic Individuals, J. Biol. Chem. **121**:457, 1937.

Guanidoacetic-acid was determined by the application of the Sakaguchi reaction to samples from which the arginine had been removed by prior treatment with arginase. Arginine was determined by measuring the difference in intensities of the Sakaguchi reactions produced before and after treatment of the sample with arginase. The procedures of Hoberman[5] were used for the preparation of samples of urine and plasma dialysates. The final color development was made by the technique of Dubnoff and Borsook.[6] The values for creatine and guanidoacetic acid were corrected for their slight interference with each other when both were determined.[7]

The serum creatine and creatinine were determined on tungstic acid filtrates of serum using the methods described by Peters[3] followed by the adsorption procedure of Hare.[8]

Samples of rectus abdominis muscle were obtained in most instances within three hours after death. The sample was homogenized in tungstic acid (100 mg. wet weight of muscle, 8 ml. of water, 1 ml. of 10% sodium tungstate, and 1 ml. of 2/3 N sulfuric acid) with the aid of the homogenizer of Potter and Elvehjem.[9] The mixture was then centrifuged and the creatine in the supernatant fluid determined by the procedure of Peters.[3]

RESULTS

Effect of the Simultaneous Ingestion of Arginine, Aminoacetic Acid, and Methionine Upon the Excretion of Creatine and Creatinine in Premature Infants.—These data were obtained to test the possibility that the relatively low creatinuria of the premature infant might be due to an insufficient dietary supply of the precursors of creatine, namely, arginine, aminoacetic acid, and methionine. The infants were fed the stock diet and the basal creatine, creatinine, and nitrogen excretion determined. One-fourth of the dietary nitrogen was then replaced by an equimolecular mixture of *l*-arginine hydrochloride, aminoacetic acid, and *dl*-methionine, the total nitrogen content of the diet remaining unchanged. The carbohydrate content of the diet was adjusted to maintain the caloric intake. Sodium citrate was added to the diets in an amount equivalent to the arginine hydrochloride. The studies were continued during an after-period on the original diet. In these studies, the creatine and creatinine determinations were made with the enzymatic procedure. A variable amount, of the order of 5 to 15%, of the material in the urine of premature infants which reacts with alkaline picrate solutions is not creatine or creatinine as measured by the enzymatic procedure. The excretion of these chromogens was not affected by the dietary regimens employed. The results of these observations are shown in Table 1.

The ingestion of a mixture of arginine, aminoacetic acid, and methionine produced no increases in creatinine. The effects on creatinuria were variable. In four infants (B, S, F, M) whose total nitrogen intake was maintained constant, there was actually a decrease in creatine excretion during the first days of amino acid ingestion. Since this decrease did not occur for Infant C, the only infant whose

5. Hoberman, H. D.: The Determination of Guanidoacetic Acid and Arginine in Human Urine and Serum, J. Biol. Chem. **167**:721, 1947.

6. Dubnoff, J. W., and Borsook, H.: A Micromethod for the Determination of Glycocyamine in Biological Fluids and Tissue Extracts, J. Biol. Chem. **138**:381, 1941.

7. Sims, E. A. H., and Seldin, D. W.: Reabsorption of Creatine and Guanidoacetic Acid by the Renal Tubules, Am. J. Physiol. **157**:14, 1949.

8. Hare, R. S.: Endogenous Creatinine in Serum and Urine, Proc. Soc. Exper. Biol. & Med. **174**:148, 1950.

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TABLE 1.—*Daily Excretion of Creatine, Creatinine, and Total Nitrogen Following the Simultaneous Ingestion of Arginine, Aminoacetic Acid, and Methionine by Premature Infants*

Patient	Birth Weight, Gm.	Age, Days	Weight, Gm.	N Intake as		Total Urinary N, Mg./Kg.	Urinary	
				Powdered Cow's Milk, Mg./Kg.	Amino Acids, Mg./Kg.		Creatinine, Mg./Kg.	Creatine, Mg./Kg.
B	1,800	18	2,140	970	0	365	13.4	3.5
		19	2,150	966	0	410	15.0	5.3
		20	2,230	931	0	403	14.3	5.2
		25	2,340	644	288	402	11.4	1.8
		26	2,350	764	366	442	13.1	1.4
		31	2,450	737	324	569	13.4	9.0
		32	2,540	706	311	638	14.6	8.1
		33	2,550	704	310	668	16.0	6.6
		37	2,650	948	0	514	13.6	7.4
		38	2,670	942	0	495	14.5	8.5
S	1,800	20	2,300	903	0	391	15.0	1.8
		22	2,370	876	0	324	11.3	3.6
		23	2,370	876	0	344	10.8	2.4
		28	2,600	594	259	304	10.7	0.7
		29	2,650	586	255	369	13.0	0.6
		30	2,690	576	250	346	12.3	0.8
		32	2,740	634	276	362	10.6	1.2
		33	2,750	632	275	406	12.5	0.9
		34	2,760	630	274	370	13.1	0.9
		38	2,780	850	0	498	15.2	3.7
		39	2,780	850	0	444	13.0	5.3
		40	2,780	850	0	438	11.7	6.7
		46	2,970	792	0	475	12.8	0.4
		47	3,000	790	0	414	14.3	0.6
		48	3,040	786	0	491	14.8	0.6
F	2,000	11	2,270	826	0	350	13.9	2.2
		13	2,400	780	0	322	12.5	5.0
		18	2,500	587	239	383	13.5	2.7
		19	2,510	586	238	364	15.0	1.1
		21	2,650	576	232	375	13.7	1.2
		25	2,740	604	248	336	12.0	1.4
		26	2,790	595	245	406	12.0	3.2
		32	2,970	828	0	376	13.1	4.5
		33	2,980	826	0	322	10.9	4.3
M	1,600	32	1,890	994	0	421	14.5	6.2
		35	2,000	940	0	335	13.4	4.6
		41	2,170	608	275	279	11.9	1.6
		42	2,200	600	272	298	11.0	1.9
		48	2,250	672	298	484	15.2	8.3
		54	2,570	912	0	366	16.5	7.6
		55	2,590	904	0	284	15.7	8.3
		56	2,610	897	0	388	15.6	7.9
E	1,800	11	1,950	842	0	333	15.3	0.0
		12	1,960	836	0	265	12.0	1.7
		13	1,990	825	0	306	14.0	3.4
		20	2,230	592	268	287	13.5	0.7
		21	2,260	584	265	348	15.6	2.0
		22	2,290	576	261	367	15.1	4.3
		29	2,570	588	264	345	15.1	4.3
		30	2,570	588	264	427	16.9	7.2
		31	2,570	588	264	392	17.1	6.1
		36	2,840	818	0	333	14.0	4.1
		37	2,940	798	0	380	14.6	6.5
C *	2,000	14	2,200	746	0	281	14.0	3.7
		15	2,230	735	0	332	15.6	4.2
		24	2,400	880	280	489	14.5	6.9
		25	2,440	866	276	462	13.6	6.1
		26	2,480	852	272	488	14.7	3.8
		31	2,640	800	255	383	11.3	5.1
		32	2,670	790	252	522	14.0	6.9
		33	2,700	782	249	542	15.9	6.3
		37	2,860	818	0	387	13.9	8.2
		38	2,900	807	0	407	14.3	7.3
		39	2,940	796	0	401	13.5	5.8

* For Infant C, the amino acids were added to the previous diet. For all other infants, the amino acids were substituted for an equal amount of milk protein nitrogen.

intake of milk and therefore of preformed creatine was maintained, the drop noted may have been due to a decreased ingestion of creatine in the diet. This was calculated to contain 5 mg. of creatine per kilogram per day. After the first few days of amino acid ingestion, the creatine in the urine rose for all but Infant S to higher levels in the post-period than had existed in the pre-period. The variability of the baseline levels, the initial decrease in creatine excretion on administration of amino acids, and the smallness of the subsequent increase in relation to the size of the amino acid supplement lead, however, to the conclusion that lack of amino acid precursors of creatine in the diet is not the limiting factor determining the relatively low creatine excretion of these infants.

The urinary nitrogen was only slightly affected by the substitution of a mixture of the three amino acids for one-fourth of the basal dietary nitrogen. The average percentages and ranges of the ingested nitrogen which were excreted, for the six infants in this series of experiments, were as follows: preliminary basal period 36.9% (31.7 to 45.2%), period of amino acid ingestion 43.9% (28.4 to 65.9%), and final basal period 42.6% (31.5 to 62.5%).

Effect of the Simultaneous Ingestion of Arginine and Aminoacetic Acid upon the Excretion of Guanidoacetic Acid, Creatine, Creatinine, and Nitrogen in Infants.—The purpose of these experiments was to compare the quantities of guanidoacetic acid excreted by premature and by full-term infants on the stock diet and to then ascertain the effect of the administration of arginine and aminoacetic acid, the precursors of guanidoacetic acid. The results of such experiments, it was thought, might yield information concerning the relative abilities of premature and full-term infants to synthesize guanidoacetic acid.

Borsook, Dubnoff, Lilly and Marriott [10] have reported that the ingestion by adults of arginine and aminoacetic acid resulted in an increased excretion of guanidoacetic acid. This increase, however, was not accompanied by an increased blood level of guanidoacetic acid. Flood and Pinelli [11] have noted that in three premature infants the excretion of guanidoacetic acid was somewhat lower than in full-term infants when compared on a basis of body weight.

In the observations to be reported, after a preliminary period in which the infants were fed the basal diet, an equimolecular mixture of *l*-arginine hydrochloride and aminoacetic acid were added to the diet. Sodium citrate was included in amounts equivalent to the arginine hydrochloride. Finally, a return was made to the basal diet. The results are shown in Table 2.

The average daily excretion of guanidoacetic acid for the seven premature infants while on the basal diet was 2.5 mg. per kilogram with a range of 1.7 to 2.9 mg. The average daily excretion for four full-term infants was 2.7 mg. per kilogram with a range of 1.9 to 3.6 mg. (Tables 2 and 3). Our premature infants thus excreted as much guanidoacetic acid as did full-term infants while on the basal diet. The amounts excreted by both premature and full-term infants were about three times as high as those reported by Flood and Pinelli.[11] These authors used an adsorption procedure for removal of arginine, while we destroyed arginine by means of arginase.

10. Borsook, H.; Dubnoff, J. W.; Lilly, J. C., and Marriott, W.: The Formation of Glycocyamine in Man and Its Urinary Excretion, J. Biol. Chem. **138**:405, 1941.

11. Flood, R. G., and Pinelli, R. W.: Urinary Glycocyamine, Creatine and Creatinine: I. Their Excretion by Normal Infants and Children, Am. J. Dis. Child. **77**:740, 1949.

The ingestion of arginine and aminoacetic acid did not significantly affect the excretion of creatinine or arginine in either premature or full-term infants. No increase in the creatinuria of the premature infant was noted, but there appeared

TABLE 2.—*Daily Excretion of Guanidoacetic Acid, Arginine, Creatine, Creatinine, and Total Nitrogen Following the Ingestion of Arginine and Aminoacetic Acid by Premature and Full-Term Infants*

Patient	Birth Weight, Gm.	Age, Days	Weight, Gm.	N Intake as			Total Urinary N, Mg./Kg.	Creatinine, Mg./Kg.	Creatine, Mg./Kg.	Guanidoacetic Acid, Mg./Kg.	Arginine, Mg./Kg.
				Powdered Cow's Milk, Mg./Kg.	Arg.,* Mg./Kg.	Am., Mg./Kg.					
A	1,100	62	1,800	745	0	0	...	13.1	0.6	2.3	0.6
		63	1,850	725	0	0	...	12.7	0.4	2.3	1.4
		67	1,900	705	170	42	...	13.2	0.0	3.8	0.8
		68	1,920	698	169	42	...	13.2	0.0	3.7	1.4
		69	1,960	770	165	41	...	13.9	0.0	3.6	1.9
		74	2,200	709	0	0	...	13.3	0.2	1.6	0.8
T	1,700	31	2,030	764	0	0	347	13.8	1.4	2.8	0.7
		32	2,010	771	0	0	405	13.2	1.1	2.6	0.5
		33	2,030	764	0	0	374	9.9	1.2	2.7	0.7
		35	2,000	820	168	42	439	10.6	1.6	3.5	0.2
		36	2,010	792	167	42	462	12.7	0.9	4.0	1.0
		40	2,000	815	163	41	487	13.4	1.3	4.2	0.4
		52	2,000	946	0	0	242	10.9	1.3	1.6	2.1
		53	2,030	868	0	0	337	14.3	1.7	2.1	1.6
B	1,020	35	1,800	912	0	0	396	11.3	2.0	2.5	0.6
		36	1,820	902	0	0	460	14.9	2.6	2.9	1.0
		38	1,910	880	169	42	373	12.6	2.4	3.1	1.3
		41	1,980	859	163	41	520	14.4	4.0	4.5	0.9
		60	2,450	890	0	0	195	9.8	3.6	2.1	1.0
		62	2,480	880	0	0	231	9.9	1.5	2.0	1.7
Ar †	3,500	42	4,250	825	0	0	400	14.2	3.4	2.1	1.0
		43	4,250	799	0	0	381	15.5	2.1	1.9	1.0
		47	4,300	795	0	0	502	16.0	4.6	2.6	0.9
		48	4,330	817	135	34	515	14.8	4.7	3.0	1.5
		49	4,350	807	135	34	584	17.0	2.8	3.1	1.4
		52	4,480	823	131	33	591	16.9	6.6	3.3	1.2
		53	4,470	689	131	33	608	16.9	7.6	3.8	1.1
		54	4,440	824	0	0	496	16.1	7.2	2.6	1.1
		59	4,600	826	0	0	517	15.1	5.6	2.2	0.8
		65	4,820	874	0	0	456	15.2	2.1	1.7	1.1
		67	4,840	871	0	0	543	15.7	4.0	2.3	1.1
L †	2,900	69	5,040	830	0	0	...	14.8	10.8	3.7	...
		70	5,100	825	0	0	...	12.9	11.6	3.7	...
		71	5,150	810	0	0	...	12.8	11.3	3.4	...
		74	5,100	790	132	33	...	14.0	13.9	5.6	...
		75	5,100	790	132	33	...	14.7	14.4	5.7	...
		79	5,170	844	130	32	...	16.6	19.9	5.9	...
		82	5,370	824	125	31	...	14.4	16.6	5.0	...
		89	5,450	801	0	0	...	12.6	11.0	3.3	...
		90	5,460	795	0	0	...	12.7	11.2	3.3	...

* Arg. indicates *l*-arginine hydrochloride; Am., aminoacetic acid.
† Full-term infants.

to be an increase in the quantity of creatine excreted by the two full-term infants amounting to an average of 2 mg. per kilogram per day for Infant Ar and 5 mg. per kilogram per day for Infant L (Table 2).

The ingestion of arginine and aminoacetic acid resulted in an increased excretion of guanidoacetic acid in both the premature and the full-term infants, the average increase ranging from 1.1 to 1.4 mg. per kilogram for the premature infants and 1.1 and 2.0 mg. per kilogram for the full-term infants.

In two infants, premature Infant C (not shown in Table 3) and full-term Infant A, the serum levels of guanidoacetic acid were determined before, during, and subsequent to the ingestion of the amino acids. The following results were obtained:

	Infant C, Mg./100 Cc.	Infant A, Mg./100 Cc.
Before	0.45	0.24
During	0.48	0.22
Subsequent	0.49	0.21

TABLE 3.—*Excretion of Guanidoacetic Acid, Creatine, and Creatinine Following the Ingestion of Guanidoacetic Acid and Methionine by Premature and Full-Term Infants* *

Patient	Birth Weight, Gm.	Age, Days	Weight, Gm.	Amino Acid Intake as GA, Mg.	Amino Acid Intake as Meth, Mg.	Creatinine, Mg.	Creatine, Mg.	GA, Mg.	Cumulative Recovery of Ingested GA as Creatine, %	Cumulative Recovery of Ingested GA as GA, %
S	1,400	38		0	0	19.2	1.4	2.3	0.0	0.0
		39		0	0	26.0	0.1	3.3	0.0	0.0
		41	1,650	110	141	25.0	3.7	13.1	2.4	9.4
		42		0	0	23.4	5.8	4.0	6.5	10.5
		43		0	0	29.3	3.6	4.6	8.8	12.1
J	1,300	38		0	0	27.8	6.4	5.6	0.0	0.0
		39		0	0	36.9	6.8	5.3	0.0	0.0
		41	1,900	123	157	32.4	25.1	21.1	13.4	12.7
		42		0	0	31.1	17.3	5.8	21.2	12.9
		43		0	0	35.3	16.6	6.1	28.4	13.4
Ga	1,600	15		0	0	30.8	3.6	5.8	0.0	0.0
		16		0	0	33.9	3.7	5.6	0.0	0.0
		18	2,130	134	171	29.0	16.0	19.5	4.2	10.3
		19		0	0	28.3	9.2	4.5	7.9	10.3
		20		0	0	29.2	6.4	4.5	10.1	10.3
G	1,500	37		0	0	37.3	8.8	5.6	0.0	0.0
		38		0	0	34.8	4.8	4.7	0.0	0.0
		40		0	0	29.9	7.2	5.6	0.0	0.0
		41	2,150	134	172	24.5	14.9	13.9	5.3	6.4
		42		0	0	26.3	10.3	4.8	7.6	6.4
		43		0	0	37.6	10.3	6.6	9.9	7.4
A †	3,500	70		0	0	69.5	25.7	9.2	0.0	0.0
		75		0	0	73.1	10.0	8.3	0.0	0.0
		77		0	0	76.0	19.2	10.1	0.0	0.0
		78	4,840	247	315	69.3	65.0	95.8	16.9	35.0
		79		0	0	82.5	65.0	12.2	33.8	36.2
		80		0	0	71.5	49.3	10.4	45.0	36.7
R †	2,800	80		0	0	78.0	33.2	13.0	0.0	0.0
		82		0	0	91.1	37.7	16.3	0.0	0.0
		83	5,070	257	328	82.0	71.6	128.5	14.9	44.4
		84		0	0	95.0	67.5	16.3	26.0	46.1
		85		0	0	88.5	62.5	15.5	35.4	46.4

* GA indicates guanidoacetic acid; Meth., *dl*-methionine.
† Full-term infants.

These results are similar to the findings of Borsook and Dubnoff that the increased excretion of guanidoacetic acid, following the ingestion of arginine and aminoacetic acid, was apparently not accompanied by increases in blood level.

Effect of the Simultaneous Ingestion of Guanidoacetic Acid and Methionine upon the Excretion of Guanidoacetic Acid, Creatine, and Creatinine.—The only known pathway for the metabolism of guanidoacetic acid is its methylation by methionine with the formation of creatine. Administered guanidoacetic acid may thus be either

excreted unchanged, stored unchanged, or methylated to creatine. In these experiments, a single dose of an equimolecular mixture of guanidoacetic acid and *dl*-methionine was administered to four premature and two full-term infants. The amounts administered were equivalent to the amounts of creatine given to infants in the creatine-tolerance study (to be described). Assuming that all of the guanidoacetic acid and methionine administered were converted to creatine, it would amount to the ingestion of 83 mg. of creatine per kg.$^{0.75}$.

The data obtained are presented in Table 3. A decided difference between the behavior of premature infants and that of full-term infants may be noted. In the four premature infants studied, the percentage of the ingested guanidoacetic acid which was recovered unchanged in the urine after 24 hours varied from 6 to 13%, with an average of 10%. In the two full-term infants, the urinary guanidoacetic acid excreted, unchanged in 24 hours, was 35 and 44%, with an average of 40% of the ingested dose.

After 72 hours, the premature infants excreted from 9 to 28% of the ingested guanidoacetic acid as creatine, with an average excretion of 14%. The full-term infants excreted 35 and 45% of the ingested guanidoacetic acid as creatine, with an average value of 40%. Considering the total recovery of the ingested guanidoacetic acid at the end of 72 hours as both creatine and guanidoacetic acid, the premature infants excreted from 17 to 42%, with an average of 25%, whereas the full-term infants each excreted 82%. It should also be noted that practically all of the additional guanidoacetic acid was excreted in 24 hours, while the excretion of creatine was prolonged.

If similar amounts of creatine had been excreted by the premature and full-term infants, this would have indicated a lack of either guanidoacetic acid or methionine in the premature infant. Since the creatine excretion of the premature remained lower than in the full-term infants, we again have evidence that a lack of precursors of creatine is not the limiting factor.

It also seems probable that the relatively low creatinuria of the premature infant is not due simply to a decreased rate of methylation of guanidoacetic acid. If the latter had been true, one might have expected that the premature infant would have excreted relatively more of the administered dose of guanidoacetic acid than the full-term infant. The reverse occurred. The more efficient kidney function of the full-term infant as compared with the premature infant might explain the greater excretion of guanidoacetic acid by the full-term infant during the first 24 hours. It cannot explain, in the absence of other factors, why the premature infant did not continue to put out guanidoacetic acid for a more extended period of time.

One must assume, then, that either the premature infant has a great ability to store this compound, or that guanidoacetic acid is rapidly methylated in both the premature and the full-term infants and that the premature infant has a greater capacity to store the creatine thus formed. The ability of the infants to store ingested creatine was therefore examined, and the results are presented in the next section.

Effect of the Ingestion of Creatine by Premature and Full-Term Infants upon the Excretion of Creatine and Creatinine.—The difference between the creatinuria of premature and that of full-term infants may be a reflection of the greater ability of the premature infant to store creatine.

Marples and Levine [1b] have reported that full-term infants, who exhibit a spontaneous creatinuria, have a low tolerance for ingested creatine. From 55 to 65% of the amount ingested was excreted in the urine as creatine in the first 24 hours and 63 to 82% in 48 hours.

TABLE 4.—*Creatine-Tolerance Tests in Premature and Full-Term Infants*

Patient	Birth Weight, Gm.	Age, Days	Weight, Gm.	Creatine Ingested, Mg.	Urinary		Cumulative Recovery of Ingested Creatine, %
					Creatinine, Mg.	Creatine, Mg.	
S	1,700	16	1,800	0	22	8	0
		17		0	22	7	0
		18		128	20	49	32
		19		0	24	26	47
T	1,500	39	2,100	0	36	2	0
		40		0	30	3	0
		41		147	38	56	36
		42		0	27	14	44
		43		0	26	9	48
C	1,600	22	2,200	0	30	12	0
		23		0	27	12	0
		24		151	28	60	32
		25		0	32	29	43
		26		0	37	26	52
Ca	1,700	33	2,200	0	27	2	0
		34		0	34	1	0
		35		150	30	49	31
		36		0	30	15	40
		37		0	36	6	43
Cl	1,400	42	2,200	0	23	8	0
		43		0	32	14	0
		44		150	29	59	32
L	1,500	83	3,700	0	57	17	0
		84		0	60	21	0
		85		298	58	118	43
		86		0	60	53	58
		87		0	64	34	65
M *	3,250	240	8,000	0	101	36	0
		241		0	102	39	0
		242		415	116	208	56
		243		0	101	92	69
		244		0	101	66	76
Car *	3,150	234	8,600	0	100	35	0
		235		0	106	28	0
		236		435	114	289	59
		237		0	110	79	70
		238		0	111	49	74
Le *	2,900	89	5,700	0	69	60	0
		90		0	69	61	0
		91		295	91	239	60
		92		0	78	83	68
		93		0	73	70	71

* Full-term infants.

In the observations to be reported, creatine was fed to infants in a single dose (83 mg. per kg.$^{0.75}$). Twenty-four-hour urine samples were collected before and subsequent to the ingestion of the creatine. The results are shown in Table 4. In the three full-term infants studied, the recovery of creatine in the urine (56 to 60% of the ingested dose in 24 hours) was almost identical to that reported by Marples

and Levine,[1b] who employed similar doses and observed infants ranging in weight from 2,900 to 7,900 gm.

The excretion of creatine (as creatinine) by the premature infants on the basal diet (calculated from Tables 1 to 4) varied from 0.0 to 27.0% of the total creatinine. It can be seen that in several instances more creatine was excreted by the premature infant than had been reported previously.[12] However, the results are in agreement with the more extensive studies of Marples,[1c] who noted that when the protein intake of premature infants was increased from 3.1 gm. to 5.2 gm. per kilogram per day, an increased creatinuria resulted. In our studies, the infants were fed a high protein diet containing approximately 5.0 to 6.0 gm. of protein per kilogram per day.

It seems clear then that premature infants, in addition to having a lower rate of creatine excretion under normal dietary conditions, also excrete a lower percentage

TABLE 5.—*Creatine Content of Human Muscle (Rectus Abdominis) During Fetal Development*

Biopsy	Birth Weight, Gm.	Muscle Creatine, Mg./100 Gm. Wet Weight
1	15	33
2	400	118
3	560	173
4	900	170
5	925	184
6	1,000	186
7	1,050	220
8	1,095	184
9	1,225	195
10	1,330	130
11	1,380	177
12	1,460	188
13	1,850	231
14	1,880	244
15	1,900	218
16	2,030	215
17	2,250	214
18	3,010	258
19	3,750	216

of ingested creatine. These results would be consistent with the hypothesis that the premature infant is relatively "unsaturated" with respect to his creatine content, as compared with the full-term infant, and may be capable of storing comparatively greater quantities of this compound.

No appreciable percentage of the ingested creatine was excreted as creatinine, by either the full-term or the premature infants.

Creatine Content of the Muscle During Fetal Development.—To obtain data on the creatine content of the muscles, biopsy specimens of the rectus abdominis were taken from 17 premature and 2 full-term infants who were born dead or died shortly after birth. None of these infants had received milk feedings. The values obtained are shown in Table 5. For the premature infants, the creatine content of the muscle, calculated on the basis of milligrams per 100 gm., wet weight, gradually increases with the birth weight. For four infants, between 400 and 925 gm., the

12. Footnote 1*a* and *b*.

average creatine content was 161 mg. per 100 gm.; for seven infants, between 1,000 and 1,460 gm., 183 mg., and for five infants, between 1,850 and 2,250 gm., 224 mg. The two full-term infants showed values of 258 and 216 mg. per 100 gm. From these data, it would appear that the greater the degree of prematurity, the less the creatine content of the muscle and perhaps the greater the capacity to store creatine after birth.

Effect of Renal Function on Creatine and Creatinine Excretion.—In view of known differences in kidney function of premature and full-term infants,[13] it seemed

TABLE 6.—*Creatine and Creatinine Values of Serum and Urine of Premature and Full-Term Infants*

Patient	Birth Weight, Gm.	Age, Days	Weight, Gm.	Serum Creatinine, Mg.	Serum Creatine, Mg.*	Urine Creatinine, Mg./24 Hr.	Urine Creatine, Mg./24 Hr.*	Creatinine Clearance, Cc./Min./1.73 Sq. M.†	Creatine Clearance, Cc./Min./1.73 Sq. M.†
Se	1,020	43	1,700	0.47	0.82	23.1	12.4	43.2	13.3
Wi	1,060	66	1,900	0.33	0.56	21.6	5.5	51.1	7.6
Ar	1,080	62	1,800	0.46	0.22	18.5	0.3	33.7	1.1
Sch	1,030	55	2,000	0.38	0.75	18.5	4.6	37.5	4.7
Se	1,390	25	1,500	0.51	0.57	12.5	0.6	23.5	1.0
Hu	1,390	30	1,670	0.62	0.60	16.2	2.7	22.9	4.0
Wo	1,330	38	1,870	0.33	0.90	28.1	2.8	69.0	2.5
Ga	1,590	20	1,690	0.65	1.25	22.6	5.8	30.6	4.1
Ga	1,590	25	1,730	0.44	0.71	23.8	2.2	46.8	2.6
Al	1,530	26	2,120	0.46	0.75	26.1	5.4	42.2	5.3
Br	1,670	30	2,000	0.45	0.75	23.9	1.3	41.0	1.3
Si	1,700	12	1,730	0.52	0.80	16.2	4.9	27.0	4.9
Sh	1,680	16	1,980	0.46	0.84	17.1	1.6	28.9	1.5
Tr	1,650	27	1,960	0.45	0.74	22.6	1.1	38.9	1.1
Sa	1,700	27	2,140	0.45	0.60	17.4	1.8	28.6	2.2
Pi	1,730	34	2,000	0.53	0.32	20.9	0.0	30.4	0.0
Co	1,750	49	2,430	0.27	0.65	28.3	2.3	70.0	2.4
Cr	1,850	35	2,220	0.38	0.61	28.7	4.6	54.0	5.4
De	1,880	14	1,790	0.48	1.24	15.2	4.2	26.6	2.8
Ma	1,890	15	2,190	0.48	0.83	26.0	10.1	39.0	8.8
Ch	1,900	16	2,000	0.60	0.83	18.1	1.6	23.2	1.4
Br	2,080	6	2,010	0.61	0.93	18.0	5.6	22.7	4.7
Shl‡	3,100	100	4,900	0.22	0.75	61.0	56.6	110.0	29.8
Ra‡	2,820	93	5,070	0.33	0.83	76.8	27.4	90.0	12.7
Le‡	2,900	89	5,450	0.25	0.91	56.9	52.7	83.0	21.1

* Calculated as creatinine.

† Clearances were corrected on the basis of surface area. Surface area (Klein, A. D., and Seammon, R. E.: Proc. Soc. Exper. Biol. & Med. **27**:456, 1930) was calculated by the formula $5.188 \times$ wt. in $gm.^{0.75}$.

‡ Full-term infants.

advisable to measure the clearances of creatine and creatinine by premature and full-term infants. Creatine and creatinine clearances were therefore obtained in an effort to at least partially evaluate the possibility that the excretory ability of the premature infant might be of some importance in conditioning their low creatinuria. In these observations, two consecutive 24-hour collections of urine were obtained, with a single postabsorptive blood sample drawn at the end of the collection period. Serum and urinary creatine and creatinine were both determined by the adsorption

13. (*a*) Barnett, H. L.: Kidney Function in Young Infants, Pediatrics **5**:171, 1950. (*b*) Rubin, M. I.; Bruch, E., and Rapoport, M.: Maturation of Renal Function in Childhood: Clearance Studies, J. Clin. Invest. **28**:1144 1949.

procedure of Hare [8] and the respective clearances calculated. Data from the 22 premature and 3 full-term infants studied are presented in Table 6. All premature infants weighed less than 2,500 gm. at the time of observation.

The values for the creatine excretion of the premature infants in this group, when calculated as per cent of total creatinine, are similar to those reported in the previous sections. They range from 0.0% to 35%, with an average of 14%. The values for the three full-term infants ranged from 26% to 48%.

The serum creatine values in the premature infants ranged from 0.22 mg. to 1.25 mg. per 100 cc., with an average of 0.74 mg. The serum creatine values of the three full term infants ranged from 0.69 mg. to 0.91 mg. per 100 cc.

The serum creatinine values in the premature infants ranged from 0.27 mg. to 0.65 mg. per 100 cc., with an average of 0.47 mg. The serum creatinine values of the three full-term infants ranged from 0.22 mg. to 0.33 mg. per 100 cc.

In order to calculate the creatinine and creatine clearances, it has been assumed that since the babies were fed at four-hour intervals, there was relatively little fluctuation from the serum levels in the postabsorptive state. It was also felt that errors in the technique of collection of urine would be minimized by the length of the collection period and by averaging the values of the two 24-hour specimens. Accepting the limitations on the accuracy of these calculations imposed by the foregoing assumptions, the creatine and creatinine clearances of the premature and full-term infants studied were compared. In view of the work recently presented by Mattar and co-workers,[14] showing that the endogenous creatinine clearance of premature and of full-term infants is comparable to the inulin clearance, it is permissible to think of the creatinine clearances in the table as a measure of the glomerular filtration rates of the premature and the full-term infants.

The creatinine clearances of the premature infants ranged from 23 to 70 cc. per minute per 1.73 square meters of body surface, with an average of 38 cc. per minute per 1.73 square meters. In the full-term infants, the values fell above the upper extreme of the premature group. However, too few infants have been studied to warrant calculating an average. These figures are in agreement with the work of Barnett and co-workers [15] and Rubin and co-workers,[13b] who have shown that the glomerular filtration rate of the premature infant is lower than that of full-term infants who are beyond the newborn period.

The ratio of creatine clearance to creatinine clearance gives a measure of that fraction of filtered creatine which escapes tubular reabsorption. The values (which were calculated from Table 6) in full-term infants (0.14 to 0.30) are in the same range as those of the premature infants (0.0 to 0.37). This means that at the rate at which creatine is filtered by the glomeruli of the premature infant's kidney a fraction similar to that in the full-term infant is excreted and that similar fractions of the filtered creatine are reabsorbed in the premature and the full-term infant.

14. Mattar, G.; Barnett, H. L.; McNamara, H., and Lauson, H. D.: Measurement of Glomerular Filtration Rate in Children with Kidney Disease, J. Clin. Invest. **31**:938, 1952.

15. Barnett, H. L.; Hare, W. K.; McNamara, H., and Hare, R. S.: Influence of Postnatal Age on Kidney Function of Premature Infants, Proc. Soc. Exper. Biol. & Med. **69**:55, 1948. Barnett, H. L.; Hare, K.; McNamara, H., and Hare, R.: Measurement of Glomerular Filtration Rate in Premature Infants, J. Clin. Invest. **27**:691, 1948.

COMMENT

The present theories concerning the origin and metabolism of creatine are reviewed by Peters and Van Slyke.[16] Guanidoacetic acid is synthesized in the kidney from arginine and aminoacetic acid. The guanidoacetic acid is transported to the liver, where it is methylated to form creatine, methionine serving as the methyl donor. The creatine is transported to the muscle, where it exists in equilibrium with phosphocreatine. The urinary creatinine is derived from tissue creatine or more probably from phosphocreatine.[17] In man, creatinine is excreted mainly by glomerular filtration, although increases in the plasma levels over the normal results in tubular secretion. Creatine also appears in the glomerular filtrate, but is completely reabsorbed by the tubules unless the concentration of creatine in the plasma exceeds approximately 0.6 mg. per 100 cc.

With these facts in mind, one may postulate that the relatively low creatinuria of the premature infant might result from a number of different causes.

1. The premature infant may have a lowered ability to synthesize creatine. This may be due to (*a*) a lack of the amino acid precursors of creatine (arginine, aminoacetic acid, and methionine), (*b*) a lowered ability to synthesize guanidoacetic acid, or (*c*) a lowered ability to methylate guanidoacetic acid.

2. The premature infant may have a relatively greater ability to store or utilize creatine.

3. The premature infant may have a higher kidney threshold for the excretion of creatine. This would result in a rise in the level of creatine in the serum and might induce a greater storage of creatine or inhibit some step in the synthesis of creatine.

The observations which we have recorded suggest that dietary sources of arginine, aminoacetic acid, and methionine are not the limiting factors determining the low excretion of creatine by the premature infant. The absence of definite increases in the creatinuria following the ingestion of large doses of these amino acids indicates that factors other than the quantities of these amino acids available to the organism are responsible.

With respect to the possibility that the premature infant has a lowered ability to synthesize guanidoacetic acid, only indirect evidence is available. The data presented on the basal level of excretion of guanidoacetic acid in premature and full-term infants indicate that an appreciable amount is present in all infants examined. Both premature and full-term infants respond to the administration of arginine and aminoacetic acid by a similar increase in the amounts of guanidoacetic acid excreted. The mechanism responsible for this increase cannot be stated unequivocally. It might be a reflection of the increased synthesis of guanidoacetic acid; however, the possibility exists that aminoacetic acid might block the reabsorption of guanidoacetic acid [7] and creatine.[18] On the other hand, this interpretation of our results merely

16. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Interpretations, Ed. 2, Baltimore, Williams and Wilkins Company, 1946. Vol. 1, p. 897.

17. Borsook, H., and Dubnoff, J. W.: The Hydrolysis of Phosphocreatine and the Origin of Urinary Creatinine, J. Biol. Chem. **168**:493, 1947.

18. Pitts, R. F.: A Renal Reabsorptive Mechanism in the Dog Common to Glycine and Creatine, Am. J. Physiol. **140**:156, 1943.

in terms of kidney function is not supported by our data, since no increase in the excretion of creatine was observed in the premature infants concomitant with the increase in excretion of guanidoacetic acid. Our observations thus offer no definite evidence concerning the relative rates of synthesis of guanidoacetic acid in premature and in full-term infants, but do indicate that guanidoacetic acid is excreted by the premature infant in significant amounts and that both types of infants respond similarly to the ingestion of the precursors of guanidoacetic acid.

More evidence is available concerning the ability of fetuses of animals to methylate guanidoacetic acid. In vitro studies have indicated that slices prepared from the livers of adult and embryonic guinea pigs and rabbits were equally effective in the synthesis of creatine.[19] In other experiments,[20] it has been shown that in appropriately fortified homogenates of liver, preparations from adult and embryonic guinea pigs were again equally effective in the synthesis of creatine.

The administration of guanidoacetic acid and methionine to premature and to full-term infants resulted in an increased excretion of creatine in both. The increased excretion of creatine in these infants cannot be entirely explained on the basis of a competition in the renal tubules for the reabsorption of creatine and guanidoacetic acid, since the excretion of creatine was prolonged for at least three days; significant amounts of guanidoacetic acid were excreted only during the first 24 hours following the administration of this compound. In addition, Sims [7] could not demonstrate that increased serum levels of guanidoacetic acid increased the excretion of creatine. Both premature and full-term infants are therefore capable of methylating guanidoacetic acid.

The lower percentage of the ingested guanidoacetic acid excreted as creatine by the premature infant cannot be taken as evidence that the premature infant methylates this compound at a slower rate than the full-term infant, since the premature infant also excretes a lower percentage of ingested creatine.

These in vitro and in vivo data, taken together, make it appear probable that the ability to methylate guanidoacetic acid is well developed in the premature infant.

The possibility that the low rate of excretion of creatine in premature infants was due to an increased ability to store or utilize creatine was investigated by determining the ability of infants to retain ingested creatine and by the analyses of the creatine content of the muscle during various stages of fetal development. It was thought that if the premature infant had a greater ability to store creatine, a larger percentage of a standard dose of creatine should be retained by these infants as compared with the full-term infants. It was also thought that, as a corollary, the creatine content of the muscle of the premature infant should be less than that in the muscle of full-term infants, assuming that the muscle is the main storage organ for the ingested creatine.

Our observations show that these conditions do obtain in these infants, suggesting that the hypothesis that premature infants have a greater ability to store creatine may be true. This interpretation receives additional support from the results

19. Cohen, S.: The Synthesis of Creatine by Preparations of Liver from Embryos and Adults of Various Species, J. Biol. Chem. **193**:851, 1951.

20. Cohen, S.: A Study of the Synthesis of Creatine by Liver Preparations, J. Biol. Chem. **201**:93, 1952.

obtained following the ingestion of guanidoacetic acid and methionine. The premature infants retained a much larger percentage of the ingested guanidoacetic acid than did the full-term infants, suggesting that the premature infant has a great ability to store either the guanidoacetic acid or the creatine formed from it. This interpretation also fits with the known facts about the increased retention of nitrogen, calcium, and phosphorus [21] by the premature infant as compared with the full-term infant.

Any influence which the kidney of the premature infant might exert in decreasing the creatinuria relative to the full-term infant should be explainable by the presence of a decreased rate of glomerular filtration or a relatively increased rate of tubular reabsorption of creatine in the premature infant. It has been shown that the glomerular filtration rate of the premature infant, even when compared on the basis of surface area, is much less than that of the full-term infant. No data are available on the actual reabsorptive capacity of the renal tubules of the premature and the full-term infants with respect to creatine. However, our data suggest that the average fraction of filtered creatine excreted in the urine is approximately the same in the premature and the full-term infants. Since the quantity of creatine filtered by the premature infant is much less than by the full-term infant, the quantity of creatine excreted is correspondingly diminished.

In the presence of a diminished filtration rate in the premature infant, it seems reasonable to suppose that the serum creatine and creatinine levels might be higher than in the full-term infant. This condition does obtain with respect to the serum creatinine levels of these infants. However, we found that the serum creatine levels of the premature and full-term infants studied were in the same range. In addition, in the two premature infants who excreted no creatine in the urine, the serum creatine levels were the lowest observed. We have, therefore, concluded that though diminished glomerular filtration is present in the premature infant, it cannot alone account for the lower creatinuria.

The problem appears to revolve around the importance of the various factors regulating the serum creatine level in premature and in full-term infants. The anabolic requirement of muscle and perhaps other tissues, as well as the excretory capacity of the kidney, appear to be involved. It is not possible from the data collected in these studies to measure precisely the relative importance of these factors. The problem should be amenable to isotope techniques, such as have been employed to measure, simultaneously, the rates of removal of inorganic iodide from the blood by the kidney and the thyroid gland.[22]

SUMMARY

The creatinuria of the premature infant was not appreciably increased by the feeding of a mixture of arginine, aminoacetic acid, and methionine.

The basal excretion of guanidoacetic acid is similar in premature and in full-term infants and is increased in both by the ingestion of arginine and aminoacetic acid.

21. Benjamin, H. R.; Gordon, H. H., and Marples, E.: Calcium and Phosphorus Requirements of Premature Infants, Am. J. Dis. Child. **65**:412, 1943. Gordon, H. H.; Levine, S. Z.; Wheatley, M. A., and Marples, E.: Respiratory Metabolism in Infancy and in Childhood: The Nitrogen Metabolism in Premature Infants—Comparative Studies of Human Milk and Cow's Milk, Am. J. Dis. Child. **54**:1030, 1937.

22. Nitowsky, H. M., and Puck, T. T.: A Modified Radioiodine Test for Thyroid Function, J. Lab. & Clin. Med. **39**:824, 1952.

When guanidoacetic acid and methionine are given, the premature infant excretes a smaller fraction of the dose as guanidoacetic acid and creatine than does the full-term infant.

When creatine is fed, the premature infant again excretes a smaller fraction of the dose than does the full-term infant.

Muscle biopsies of infants, either stillborn or dying at birth, show that the more premature infants have less creatine in muscle.

Studies of renal excretion of creatine and creatinine show that the premature infant has a creatinine clearance much lower than that of the full-term infant, despite which the average serum creatine levels of the two infants are similar.

In conclusion, these data are in agreement with the hypothesis that the premature infant excretes less creatine than the full-term infant because of a greater capacity to store or utilize creatine. This may possibly be enhanced by the decreased glomerular filtration of creatine in the premature infant.

AGGLUTINATION STUDIES IN VISCERAL LARVA MIGRANS

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VISCERAL larva migrans, recently described by Beaver and his associates, presents an origin for a group of the extreme eosinophilias found in children.[1] The actual demonstration of larvae or ova in a liver biopsy appears necessary to make the diagnosis.[2] Since such a procedure is necessarily limited, an alternative method of diagnosis would be advisable. The following case is presented to show a probable relation between such an eosinophilic condition and lung infiltrations with serological evidence of parasitic infection.

REPORT OF CASE

K. C., a 28-month-old white boy, was first seen on Sept. 19, 1952, referred from the surgical service for an evaluation prior to surgery on a left indirect inguinal hernia. The routine blood cell count revealed a leucocyte count of 49,200, with 75% eosinophiles in the differential count.

This boy was the third of four children. The mother's preportal course was uneventful and delivery was normal. At birth the baby weighed 8 lb. (3,630 gm.). The subsequent early postnatal course was without incident. He walked at the age of 11 months, talked at 24 months and was said to have 10 teeth at 1 year.

From the age of 5 months, however, he was repeatedly seen in the clinic for frequent respiratory infections. The first episode, an otitis and pharyngitis, was treated with three injections of penicillin. At the age of 9 months, he was seen following a febrile convulsion. Examination revealed a bilateral otitis and a tonsillitis which was treated with three penicillin injections. At the age of 10 months, a pharyngitis was diagnosed and treated with a liquid sulfonamide preparation. At the age of 11 months, following 24 hours of vomiting and diarrhea, a pharyngitis was found to be the cause and was then treated with orally administered penicillin for two days. During the summer of 1951 he was well. At the age of 16 months, a pharyngitis with high fever was treated with two penicillin injections. At the age of 20 months, he was seen with an acute tonsillitis, aphthous stomatitis, and early otitis media. Following a poor response to penicillin by injection for four days, he was given aureomycin with good recovery. At the age of 22 months, a right otitis media was treated with the liquid sulfonamide preparation for four days. Response was not good, and the symptoms recurred. He was again given penicillin injections for three

1. Beaver, P. G.; Snyder, C. H.; Carrera, G. M.; Dent, J. H., and Lafferty, J. W.: Chronic Eosinophilia Due to Visceral Larva Migrans: Report of 3 Cases, Pediatrics **9**:7 (Jan.) 1952.

2. (*a*) Footnote 1. (*b*) Perlingiero, J. G., and György, P.: Chronic Eosinophilia: Report of Case with Necrosis of the Liver, Pulmonary Infiltrations, Anemia and Ascaris Infestation, Am. J. Dis. Child. **73**:34 (Jan.) 1947. (*c*) Zuelzer, W. W., and Apt, L.: Disseminated Visceral Lesions Associated with Extreme Eosinophilia: Pathologic and Clinical Observations on Syndrome of Young Children, ibid. **78**:153 (Aug.) 1949. (*d*) Mercer, R. D.; Lund, H. Z.; Bloomfield, R. A., and Caldwell, F. E.: Larval Ascariasis as a Cause of Chronic Eosinophilia with Visceral Manifestations, ibid. **89**:46 (July) 1950. (*e*) Behrer, M. R., and Klingberg, W. G.: Hypereosinophilia with Eosinophilic Granuloma of the Liver Associated with Ascaris Infestation, J. Pediat. **38**:635 (May) 1951. (*f*) Atmar, R. C.: Familial Eosinophilia: Report of Case with Biopsy of Liver, J. A. M. A. **115**:449 (Aug. 10) 1940.

days. At the age of 23 months, he was seen with a febrile pharyngitis of five days' duration. Treatment consisted of two three-day courses of penicillin injections. At the age of 25 months, he was treated with three penicillin injections for a bilateral otitis media. He was then well during the summer of 1952. In early September, he had an episode of acute pharyngitis and received four penicillin injections as treatment.

The laboratory and x-ray findings for our patient, K. C., are given in Table 2.

TABLE 1.—*Laboratory Findings for Ki.C., Younger Brother of Patient*

Age, Mo.	Findings on Clinic Visit	White Blood Cell Count	Differential Count *			Hemoglobin, Gm./100 Cc.
			P, %	L, %	E, %	
1	Pharyngitis, β Streptococcus	8,500	2	94	2	14.0
2½	Bronchitis, Staphylococcus aureus (chest x-ray, negative)	11,700	30	66	4	13.5
12	Routine	9,700	27	58	12	9.5

* P indicates polymorphonuclear leucocytes; L, lymphocytes; E, eosinophiles.

TABLE 2.—*Laboratory and X-ray Findings for Patient K. C.*

Hematology

Date	White Blood Cell Count	Eosinophiles, %	Hemoglobin, Gm./100 Cc.
9/18	49,200	75	9.8
9/19	38,300	84	9.7
9/19	50,200	69	10.4
10/3	63,000	71	10.4
10/20	65,000	71	11.4
11/13	53,600	72	10.1

Urinalysis

Date	24-Hour Urine Specimen Lead, Mg.
9/22-23	0.632
10/25-26	0.032

Feces

Negative for ova and parasites. Giardia lamblia noted on one occasion.

Serology

Date	Agglutination Reaction	
10/3	Toxocara canis	1:8
11/13	Toxocara canis	1:160
	Ascaris lumbricoides	1:640
	Heterophile, guinea-pig absorption	1:56
	Cephalin flocculation, 48 hr.	4+

Radiology

Date	Chest	Long Bones
9/19	Slight increase of lung markings	
10/13	Some increased lung markings throughout both lung fields, more accentuated at right base	Negative for osseous abnormality
10/27	Lung fields clear	Widened band of increased density in metaphyseal region

The initial examination showed a mild catarrhal rhinitis, which the mother stated had been present for two days. The color was pale, but the boy was alert and active. The weight was 26.5 lb. (12,020 gm.). On abdominal examination, no liver or spleen pathology or adenopathy was noted. A patent left external ring was palpable. A neurological evaluation was unremarkable.

During the two summers, the family vacationed first in northern New York State and then on Cape Cod, Mass. The remainder of the boy's life was spent only in western Massachusetts. Both parents stated that the boy had been noted on numerous occasions during the previous three months to eat dirt from the yard, paint from his bed, wood, crayons, erasers, and other objects.

The family history revealed that the maternal grandmother suffered from both hay fever and asthmatic attacks. The oldest sister, age 18 years, showed a white blood cell count of 9,050, with 3% eosinophiles. The second sister had been followed in the clinic for stuttering, as well as for an occasional upper respiratory infection. The mother stated that this girl, age 5 years, had had several attacks of asthmatic bronchitis during the previous two winters. Her white blood cell count was 7,200, with 22% eosinophiles. The youngest child, a boy age 12 months, had also been seen in the clinic for several respiratory infections. The laboratory findings for this child are given in Table 1.

During the follow-up clinic visits, supportive multivitamins and an iron preparation only were given. The parents were able to control the boy's pica after the initial visits. Within six weeks, the boy improved greatly in appetite for food and in appearance. The hernia repair had been postponed.

PREPARATION OF SPECIAL ANTIGENS

The antigens utilized in this study were prepared from freshly obtained round worms, from humans the Ascaris lumbricoides and from dogs the Toxocara canis. The worms were initially put in saline and preserved by freezing. At the time of making the antigens, the worms, following thawing, were washed in isotonic

TABLE 3.—*Ascaris Antigen Studies*

Patient	Age, Yr.	Diagnosis	White Blood Cell Count	Eosinophiles, %	Ascaris Agglutinations	
					Ascaris lumbricoides	Toxocara canis
P. B.	2	Ascariasis	7,850	2	Negative	Negative
G. T.	3½	Ascariasis	9,700	3	Negative	Negative
T. H.	4½	Ascariasis	8,700	10	Negative	Negative
P. M.	6	Ascariasis	6,050-13,800	2-9	Negative	Negative
V. M.	33	Ascariasis	7,200-12,650	2-4	Negative	Negative
R. P.	1½	Infectious lymphocytosis	12,550-22,200	1-7	Negative	Negative
M. M.	7	Rheumatic fever	7,250-11,700	0-10	Negative	Negative
S. S.	9	Routine check-up	6,450	20	Negative	Negative

saline. A fine pulp was made by mashing the specimens with a mortar and pestle. A 20% suspension in isotonic saline was prepared and this crude antigen then heated in a boiling water bath for one hour. At completion, the final volume was returned with distilled water and phenol added to make a 0.5% solution. Following filtration, the filtrate was saved and sufficient saline added to make a final 5% antigen suspension.

Standard serial dilutions of the blood sera were made to which 0.5 cc. antigen was added. The tubes were placed in a water bath at 37 C. overnight and the presence of agglutination noted. Any agglutination in the tube was considered positive.

Studies to evaluate the specificity of the antigens were undertaken. Sera from five patients with ascariasis and three patients with eosinophilia of other cause were obtained and examined. The results are presented in Table 3.

COMMENT

Beaver and his associates reviewed the literature of patients reported with extreme eosinophilia, and, analyzing these patients and their own patients, ascribed the cause to the migration of the larvae of T. canis in the human host.[1] Following ingestion of the ova in contaminated dirt, the larvae hatch in the upper section of the small intestine. The larvae then migrate into the body and circulation and are carried primarily to the liver. There may also be a phase of migration through the

lungs which produces pulmonary infiltrations. In the liver, the larvae are walled off and eosinophilic granulomas develop which are seen on laparotomy as numerous 0.5- to 6-mm. whitish nodules on the liver. Since the larva is not adapted to the human host, maturation rarely occurs.[3] Thus, prolonged retention of the larva produces results which may cause an allergic response in infants. Hypereosinophilia, hyperglobulinemia, serum sickness reaction of the heterophile test, and urticarial and wheezing symptoms are manifestations of this response. The disease is benign.

In the present patient, evidence for visceral larva migrans was suggestive. Persistent leucocytosis with extreme eosinophilia was prominent. There was a hypersensitivity to infections which resulted in 11 episodes treated with sulfonamides and antibiotics in a two-year period. A familial trend toward allergic symptomatology was noted, and a familial eosinophilia was present. The familial eosinophilia described by Atmar was related to this condition by Zuelzer, although, in most reported patients, no family history is noted.[2f]

Several examinations of this patient failed to reveal any significant enlargement of the liver or other adenopathy. Hepatic enlargement has been a consistent feature elsewhere. Chest x-rays did show pulmonary infiltrations which cleared during the observation period. The similarity to Löffler's syndrome has been noted.

Laboratory examinations revealed a heterophile titer of 1 : 56 with the guinea-pig absorption method. Silver suggested the relation of this condition to serum sickness by the reaction of the heterophile agglutinin absorption tests.[4] Hyperglobulinemia was demonstrated by Zuelzer and Apt by electrophoretic studies and by others with elevated serum globulin determinations.[5] The cephalin flocculation reaction in this patient was strongly positive and was interpreted to represent an elevated serum globulin.

The serological studies with Ascaris antigens proved interesting. In the three patients with eosinophilia and the five patients with ascariasis, infestation with A. lumbricoides, both human and dog Ascaris agglutination tests were negative. In the presented patient, an increase from 1 :8 to 1 :160 of the T. canis titer was demonstrated over a period of five and one-half weeks. The A. lumbricoides titer was markedly elevated, 1 :640.

Zuelzer and Apt performed Ascaris skin tests on five of their patients with negative results. The patient described by Mercer showed sensitivity to Ascaris extract by a positive skin test.[2d] He further recorded an observation of Zweitel that 70% of patients with Löffler's syndrome showed sensitivity to Ascaris extract. It is probable that some substance of the Ascaris worm common to all species, possibly the keratin described by Campbell in his experimental studies of A. suis, is the antigen involved in the production of this syndrome in the sensitized child.[6]

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3. Swartzwelder, J. C.: Toxocara Catis (Cat Ascarid) Infection in Man: Report of an Additional Case, J. Trop. Med. **44**:61 (May) 1941.

4. Silver, H. K.; Henderson, P., and Contopoulos, A.: Extreme Eosinophilia, Increased Blood Heterophile-Agglutination Titer, and Hyperglobulinemia, A. M. A. Am. J. Dis. Child. **83**:649 (May) 1952.

5. Footnotes 1, *2c* and *e*, and 4.

6. Campbell, D. H.: Experimental Eosinophilia with Keratin from Ascaris Suum and Other Sources, J. Infect. Dis. **71**:270 (Nov.-Dec.) 1942.

In view of the history that the patient had lived only in the northeastern section of the United States, local infestation with A. lumbricoides was unlikely. Stool examination was negative. T. canis infections of dogs are very common. It has been shown that the ova of T. canis can be easily found in most yard soils. With pica a prodromal feature, shown also by the subclinical plumbism in this patient but noncontributory to the course, ingestion of the dog Ascaris ova was possible.

SUMMARY AND CONCLUSIONS

Two features appear to be required to produce the syndrome of visceral larva migrans: pica and an allergic-hyperergic reaction. Since pica occurs commonly, and in the age group of 15 to 36 months, this syndrome would be expected to be a frequent disease. Recognition is apparent only in the hypersensitive child. A patient is presented in whom these features were present.

Evidence for visceral larva migrans is presented by a serological study with human and dog Ascaris antigens. In the absence of Ascaris lumbricoides infestation, this agglutination reaction may be considered diagnostic.

Maj. Thomas B. Smith and assistants, of the Westover Air Force Base Hospital Laboratory Service, prepared the antigens and did the other laboratory work in this study.

RISK OF DEATH FROM ASPHYXIATION IN MEASLES ENCEPHALITIS

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THE COMMONEST complications of measles, pneumonia and otitis, can nowadays be overcome by the use of chemotherapeutic agents, antibiotics, etc. Encephalitis, on the other hand, is still a dreaded complication, and rightly so, besides presenting major difficulties in treatment. The mortality rate in measles encephalitis, as will be seen from the following table,[1] is high, ranging between 10 and 50%. The pronounced variation is partly attributable to differences in diagnostic evaluation.

The symptomatology of measles encephalitis varies widely, showing all degrees of severity ranging from mild cases with listlessness or irritation of short duration, then those with more or less stuporous states, to the severest forms attended by unconsciousness and convulsions. A study of mortality statistics in the literature shows that fatal cases are concentrated in the group with convulsions and unconsciousness. This is indeed true of a series from the Stockholm Hospital for Infectious Diseases, comprising 50 cases referable to the period from 1946 to 1951, and from which it is evident too that cases in which the patients have prolonged convulsive attacks associated with unconsciousness have the poorest prognosis.

We are not concerned here with the neurologic symptomatology in measles encephalitis; rather our aim is to call attention to one fundamental cause of fatal outcomes in this disease which does not seem to have been sufficiently considered hitherto, namely, asphyxiation due to respiratory tract obstruction. Three cases of severe measles encephalitis, in which the patients were admitted in a moribund condition to the Stockholm Hospital for Infectious Diseases in the spring of 1952 and were treated successfully with the above consideration in mind, have brought this problem into the foreground. The cases in question are described below.

REPORT OF CASES

CASE I.—A 5-year-old girl fell ill with measles and exanthema on Jan. 2, 1952. One week later she was subfebrile, but in the early hours of Jan. 10 there was a severe convulsive attack with unconsciousness. At 9:30 a. m., the same day a further attack occurred with loss of

From the Stockholm Hospital for Infectious Diseases.

1. (*a*) Hamilton, P. M., and Hanna, R. J.: Am. J. Dis. Child. **61**:483, 1941. (*b*) Ford, F. R.: Bull. Johns Hopkins Hosp. **43**:140, 1928. (*c*) Litvak, A. M.; Sands, I. J., and Gibel, H.: Am. J. Dis. Child. **65**:265, 1943. (*d*) Reisman, H. A., and Rosen, A. S.: ibid. **66**:597, 1943. (*e*) Bang, J.: Bibl. læger. **133**:221, 1941. (*f*) Sawchuk, S.; LaBocetta, A. C.; Tornay, A.; Silverstein, A., and Peale, A. R.: Measles Encephalitis, Study of 50 Cases, Am. J. Dis. Child. **78**:844, 1949. (*g*) Seagle, J. B.: J. Indiana M. A. **42**:1254, 1949. (*h*) Jacobsson, E., and Holmgren, B.: Ann. pædiat. **173**:231, 1949.

consciousness, the patient being admitted to hospital one hour later. She was then enervated and cyanotic and showed dilated pupils and crepitant respiration. She was stimulated with niketharnide, and oxygen was administered, as well as 1 gm. of chloral rectally. At 11:30 a. m. she was still unconscious and had clonic convulsions of the whole left side and right deviation of the head. At auscultation of the lungs numerous soft rales were heard, particularly on the right side. Four centigrams of Hypnofen [2] was administered. By 1 p. m. the convulsions had commenced to abate, quiet periods being occasionally interrupted by clonic convulsions lasting a few minutes, particularly in the arms. At 2 p. m. there was a sudden severe deterioration, the patient becoming pulseless, cyanotic, and ceasing to breathe concurrently with a discharge of mucus from the mouth. The patient was immediately stretched out face down, with the trunk lowered; the thorax was then compressed vigorously and rhythmically, with one hand on the chest and the other on the back. In this way a copious amount of thick glassy mucus was expressed. Concurrently an aspirator was used in the nasopharynx, and oxygen was administered through the nose. After some minutes the patient breathed a few times spontaneously, and the cyanosis commenced to abate. Under continued artificial respiration a considerable amount of mucus was discharged, and after half an hour the spontaneous breathing had improved so much that artificial respiration could be discontinued, leaving only the aspiration and administration of oxygen. A temporary drainage position was effected by placing a firm pillow under the abdomen,

Mortality in Measles Encephalitis

Series	No. of Cases	No. of Deaths	Mortality, %
Hamilton and Hanna [1a]	285	58	20
Ford [1b]	125	12	10
Litvak and co-workers [1c]	56	8	14
Reisman and Rosen [1d]	20	2	10
Bang [1e]	10	5	50
Sawchuk and co-workers [1f]	50	16	32
Sawchuk and co-workers [1f]	36	10	28
Seagle [1g]	12	1	10
Jacobsson and Holmgren [1h]	48	5	10

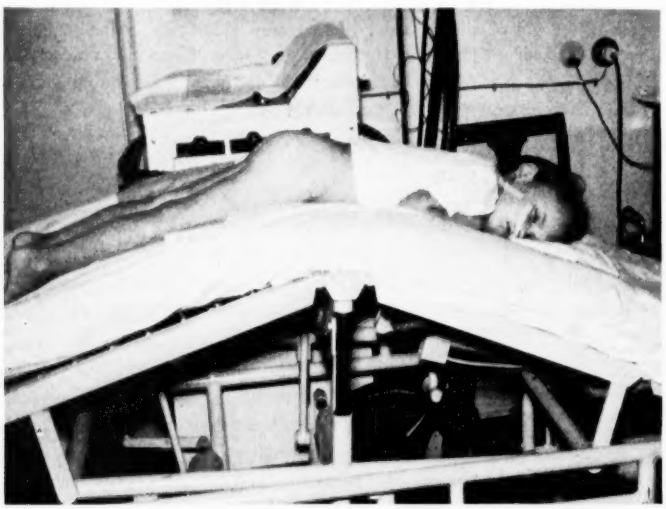
the patient being transferred after an hour or so to a special drainage bed (Figure). For the next few hours the patient remained in the drainage position, with an oxygen catheter in the nasopharynx. The convulsions, which had previously been frequent, conspicuously diminished after the treatment and consisted mostly of brief spasms in the arms and face. Four hours later no rales could be detected in the lungs, and bedside x-ray examination disclosed only "inflammatory hyperemia round the hili, without any areas of density proper." Eight hours later the patient was quiet, had no convulsions, and showed satisfactory spontaneous respiration. In the next few days there were short periods of slight tonic convulsions, at which, due to the drainage position, frothy mucus was discharged from the mouth. Subsequently no convulsions occurred, the condition remaining much the same, with stupor, inability to swallow, and pronounced irritation; not until about one month had elapsed did spontaneous activity commence to return. As of the second day the patient was given fluid subcutaneously, and then nourishment through a stomach tube as long as the stuporous condition persisted. There was a progressive improvement during the next four months, but on discharge the patient had spastic palsy of the right arm.

Case 2.—A 7-year-old boy fell ill with measles and exanthema on March 29. Two days later his temperature fell, and by April 2 the patient was afebrile. On April 3 he complained of headache, seemed drowsy, and had a temperature of 39.5 C. (103.1 F.). At about 5 p. m. the same day his mother found him lying unconscious, with fixed stare, foam on the lips, and rigidity of the whole body. Convulsive attacks continued, with tonic spasms and unconsciousness, the patient being admitted to the hospital one and one-half hours after the onset of the attacks. On admission he was enervated, cold, cyanotic, pulseless, and had respiratory standstill. He

2. Hypnofen contains allylisopropylmalonylcarbamide plus diethylmalonylcarbamide.

was immediately placed in the face-down drainage position. Artificial respiration with compression of the thorax dorsoventrad was resorted to, by which means a copious amount of mucus was expressed, further quantities being removed with an aspirator. Oxygen was administered through a tube in the nasopharynx. The condition rapidly improved, the pulse returning, the cyanosis abating, and the blood pressure rising to 110. However, the patient was still unconscious; he was kept in the drainage position, artificial respiration being continued for about half an hour until satisfactory spontaneous breathing had returned. Mucus was aspirated now and again. One hour after admission further convulsive attacks, albeit less pronounced, occurred. Chloral was administered by rectum, after which the convulsions ceased entirely. The patient regained consciousness the following day and was lucid enough to speak and to comprehend what was said to him. His condition progressively improved in the next few days and he was discharged as recovered on May 6.

Case 3.—A 4-year-old boy had measles exanthema on April 29, but was subfebrile by May 3. The following day his temperature rose to 38.4 C. (101.1 F.), but otherwise the general condi-



Special drainage bed.

tion was not affected. On April 5 the patient was quite lively in the forenoon despite a temperature of 38 C. (100.4 F.), but in the afternoon headaches developed, and he was drowsy and listless. He awoke at 9 p. m. and seemed restless and dazed. Soon afterwards he lost consciousness and was rigid throughout the body and had a fixed stare and convulsive rotation of the head to the right. There were continual convulsions; the breathing became scarcely perceptible and the color poor. Immediately before admission to hospital at 10:30 p. m. there was a severe attack of clonic convulsions of the whole body. On admission the patient was unconscious, enervated, pulseless, cyanotic, and showed no perceptible spontaneous respiration. He was placed face down, and artificial respiration was instituted by compression of the thorax, whereupon large quantities of thick glassy mucus, mixed with regurgitated gastric contents, were emptied. Aspiration was concurrently resorted to through the nose and through the pharynx, and oxygen was administered through a nasal catheter. The drainage position was retained, and thick secretion continued to be discharged. After about 40 minutes very slight irregular spontaneous breathing commenced, but progressively increased coincidentally with an improvement in the general condition. After two hours there was normal spontaneous respiration, but the patient was still unconscious. Oxygen was continuously administered and the drainage position was maintained, copious amounts of mucus escaping spontaneously. The fol-

lowing day the patient had considerably improved, recovered consciousness, and talked, but was still very irritable. Subsequently he showed progressive improvement and after three days was quite symptom-free.

COMMENT

All three patients thus lost consciousness, had severe convulsive attacks with profuse mucus formation in the respiratory tract, and a condition of cyanosis, atony, absence of any pulse, and respiratory standstill developed in them. In the first case this state developed four hours, and in the two others roughly two hours, after the onset of convulsions. In these cases the mechanism was as follows. During the convulsive attacks large quantities of thick glassy mucus were formed, which obturated the respiratory passages and prevented the return of spontaneous breathing after the attacks. The patients would have suffocated if the obstructing mucus had not been rapidly and effectively removed. In this connection the mode of procedure was based on experience acquired in drainage treatment of pharyngeal and respiratory paralysis in poliomyelitis (Engström[2a]). There, too, the same problem occurs, with obturation of the air passages by collections of secretion; and experience has shown us that artificial respiration in such cases will be of no avail unless those passages have first been freed therefrom. In the cases reported here, this was effected by immediately placing the patients face down with the trunk lowered, then giving artificial respiration by vigorously compressing the thorax, with one hand on the chest and the other on the back. When this was done, large quantities of mucus were forced out through the mouth, emptying being facilitated by concurrent aspiration through the pharynx and nasopharynx. Oxygen was administered through a nasopharyngeal catheter. After a relatively short time spontaneous breathing returned, being at first faint and irregular, but later more regular and vigorous, so that artificial respiration was presently discontinued, though not the drainage position, aspiration, and administration of oxygen. Subsequently the patients were kept in the same drainage position till the acute state had subsided. In this way considerable amounts of mucus were continuously discharged, particularly in the convulsive attacks, thus preventing respiratory tract obstruction. After this treatment, however, the convulsions were considerably milder in two cases and ceased entirely in the third. It should be emphasized that had these patients been treated in the dorsal position with aspiration through the pharynx, and artificial respiration perhaps with an apparatus of current type, most of the mucus would in all probability have remained in the respiratory passages and asphyxiation would have resulted.

The importance of restoring normal respiration as soon as possible (by means of effective drainage of the respiratory tract, administration of oxygen, and artificial respiration) is even more evident in that it probably serves to break a vicious circle as well. It is well known that asphyxia produces convulsions. The malignant symptoms of measles encephalitis consist in convulsions. The inhibited aeration during convulsive attacks results in more or less pronounced anoxia, that will rapidly endanger the patient's life if secretory obstruction of the air passages prevents the return of spontaneous breathing. Probably the severe repeated convulsive attacks in such cases are largely due to asphyxia and could be ameliorated if the latter were abolished.

2a. Engström, C. G.: A New Drainage Bed for Treatment of Bulbar Poliomyelitis, Nord. med. **47**:192, 1952.

Yet another mechanism is conceivable in the development of respiratory insufficiency and standstill in measles encephalitis. Cerebral edema, and possibly compression of the medulla oblongata (Sawchuk [11]) might produce such a severe depression of the function of the respiration center as to result in pronounced respiratory insufficiency or standstill. A further possibility lies in the administration of such large amounts of narcotics, to relieve the convulsions, that the function of the respiration center is impaired. However, the latter situation could be avoided, in our opinion, if the convulsant factor which asphyxia in itself constitutes is eliminated.

Artificial respiration with an apparatus may, however, be necessary in some cases. Before resorting to a respirator it must be insured, first and foremost, that the respiratory passages are kept free, in which connection the possibility of treating the patient in the face-down drainage position is of importance. If a respirator is used, the effect should be checked by the same diagnostic means as in respiratory paralysis due to poliomyelitis. The mode of procedure in cases in which poor spontaneous breathing persist should initially be the same as that described in the foregoing. Not until any respiratory tract obstruction has been relieved and the air passages satisfactorily freed, and if spontaneous breathing fails to return normally, will there be occasion to resort to a respirator.

As regards patients with stupor alone and no convulsions, they too should be treated in the face-down drainage position if the swallowing function is severely impaired and there is any tendency to stagnation of secretion in the pharynx.

A further important therapeutic problem in severe cases of measles encephalitis concerns the supply of nourishment, which should be effected in such a way as to eliminate as far as possible the risk of aspiration. At the Stockholm Hospital for Infectious Diseases we have supplied fluid and nourishment parenterally during the acute state, and subsequently through a stomach tube until the patients have been able to swallow.

The foregoing considerations regarding the risk of asphyxiation due to respiratory tract obstruction, which is present in severe cases of measles encephalitis, might also apply to severe encephalitic conditions of other etiology that are associated with convulsions.

SUMMARY

Asphyxiation due to secretory obstruction of the respiratory tract has not, it is pointed out, been sufficiently considered hitherto as a cause of death in measles encephalitis.

The risk of asphyxiation is accentuated in cases with loss of consciousness, repeated severe convulsive attacks, and profuse mucus formation.

The lives of three children with measles encephalitis, admitted to hospital in a moribund condition, were saved by relatively simple measures: (*a*) placing in a face-down drainage position with the trunk lowered; (*b*) manual expulsion of the thick mucus, of which large quantities were present in the air passages; (*c*) manual artificial respiration by intermittent compression of the thorax dorsoventrad till spontaneous breathing had returned.

Patients should not be given artificial respiration in an apparatus while placed in the dorsal position, since this entails a major risk of asphyxiation due to stagnation of secretion in the air passages.

Attention is drawn to the anoxemic factor as a fundamental contributory cause of the convulsions, which decrease or cease with adequate aeration.

Case Reports

ACUTE DEXTROAMPHETAMINE SULFATE POISONING

Report of a Case in a Child

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THE PURPOSE of this paper is to report a case of acute dextroamphetamine sulfate poisoning in a 2-year-old child. A review of the literature revealed one reported case of dextroamphetamine poisoning.[1]

REPORT OF CASE

R. W., a 24-month-old white boy, was admitted to George F. Geisinger Memorial Hospital and Foss Clinic five hours after having swallowed four or five of his mother's reducing tablets. Each tablet contained 10 mg. of dextroamphetamine sulfate and 15 mg. of phenobarbital. Within one-half hour after ingestion of the tablets, the child became increasingly active and "silly." Two and one-half hours after taking the tablets he was noted to have occasional clonic jerks of all extremities without loss of consciousness and to throw himself about the room aimlessly. Shortly thereafter the child vomited a small amount of fluid. He was seen by his local physician and was then referred to the hospital.[2] On arrival the child was hyperactive and unmanageable and periodically had short spells of delirium.

Physical examination at the time of admission revealed a well-developed well-nourished 2-year-old boy who appeared acutely ill. The child was hyperactive and disoriented and threw himself about wildly, whether in his mother's arms or on the examining table. His face was flushed. His pupils were widely and equally dilated, but they reacted to light. The deep tendon reflexes were symmetrically hyperactive. There were no pathological reflexes present. The rectal temperature was 100 F. The apical heart rate was 132 per minute, and the respiratory rate was 28 per minute. Findings on physical examination were otherwise normal.

The child was given 28 mg. of amobarbital (Amytal) sodium as a 2% solution by slow intravenous injection. The stomach was then lavaged with 1,000 cc. of isotonic saline solution, and a quantity of pink sediment was noted in the returned fluid. Intravenous administration of saline and dextrose was started. Following this, and because of increasing activity, the child was given intramuscularly administered phenobarbital sodium in a dose of 5 mg. per kilogram of body weight. This dose of phenobarbital was repeated on three occasions at four-hour intervals. This barbiturate was successful in keeping the child mildly sedated, but it did not produce somnolence. There was no definite change in the physical findings on repeated examinations until 24 hours after admission, when the pupils returned to normal size, and the hyperactivity began to decrease.

During the second 24-hour period of hospitalization the child was continued on intravenously administered fluids (120 cc. per kilogram of body weight per 24 hours). The dosage of intramuscularly administered phenobarbital sodium was changed to 6 mg. per kilogram of body weight, and this amount was given at six-hour intervals for three doses. The child's hyperactivity had definitely lessened by the beginning of the third hospital day. Concomitant with this change, euphoria and marked ataxia became apparent. The euphoria persisted for four days,

From the Department of Pediatrics, George F. Geisinger Memorial Hospital and Foss Clinic.

1. Mitchell, H. S., and Denton, R. L.: Overdosage with Dexedrine, Canad. M. A. J. **62**:594, 1950.

2. Referred through the kindness of Dr. Charles Straub, Middleburg.

and the ataxia persisted for five days. Both symptoms then quickly subsided, and the child was discharged to go home on the eighth hospital day (eight days after having ingested the drug). Subsequent examinations revealed the child to be perfectly well.

Findings on urinalysis were normal. The blood examination on admission showed the following: hemoglobin, 12.3 gm. per 100 cc.; red blood cell count, 4,600,000; white blood cell count, 10,200; differential count, neutrophiles 61% and lymphocytes 39%. Repeated blood cell counts on three occasions, the last one five weeks after the drug ingestion, revealed no significant change in any of the original values. Findings on spinal fluid examination were normal.

COMMENT

The group of drugs known as amphetamines are optical isomers classified pharmacologically as sympathomimetic agents. The dextrorotatory form is commonly sold as Dexedrine, the levorotatory form is rarely used by itself, while a combination of the dextrorotatory and the levorotatory form, the racemic form, is commonly known as Benzedrine. Dextroamphetamine sulfate is characterized pharmacologically by its marked central-nervous-system stimulatory effect, its relatively small adrenergic effect, and, as reported by some authors, its ability to reduce gastric motility and emptying time.[3] Amphetamine is destroyed slowly in the body, and the major portion of the amphetamine is excreted in the urine.[4] Urinary excretion accounts for 50% of the ingested dose within 48 hours.[3a] Amphetamine can cause addiction [5] or serious habituation in patients who continue to take the drug over a long period of time. However, this is not common, for a high tolerance to the racemic form of amphetamine in large doses over a prolonged period without adverse effects has been reported by numerous persons.[6]

Most of the causes of amphetamine poisoning reported to date have been due to the racemic form and have been characterized by signs and symptoms related to the adrenergic effects, for example, hypertension, tachycardia, syncope and exhaustion.[7] Dextroamphetamine has been reported as the cause of panhemocytopenia and eventual death in a patient who took large doses over a prolonged period.[1]

Dextroamphetamine sulfate is used frequently in the management of narcolepsy,[8] epilepsy,[9] behavior problems in children,[10] and obesity problems.[11] The popular

3. (*a*) Smith, Kline & French Laboratories, Dexedrine Reference Manual, Philadelphia. Harris, S. C.; Ivy, A. C., and Searle, L. M.: The Mechanism of Amphetamine-Induced Loss of Weight: A Consideration of the Theory of Hunger and Appetite, J. A. M. A. **134**:1468, 1947.

4. Goodman, L., and Gilman, A.: The Pharmocological Basis of Therapeutics: A Textbook of Pharmacology, Toxicology and Therapeutics for Physicians and Medical Students, The Macmillan Company, 1941, pp. 435-447.

5. Knapp, P. H.: Amphetamine and Addiction, J. Nerv. & Ment. Dis. **115**:406, 1952.

6. Bloomberg, W.: End Results of Use of Large Doses of Amphetamine Sulfate Over Prolonged Periods, New England J. Med. **222**:946, 1940. Bakst, H. J.: Daily Use of Benzedrine Sulfate Over a Period of 9 Years, U. S. Nav. M. Bull. **113**:1228, 1944.

7. Apfelberg, B.: A Case of Benzedrine Sulfate Poisoning, J. A. M. A. **110**:575, 1938.

8. Harper, F. T.: Narcolepsy, with Report of 4 Cases, North Carolina M. J. **6**:96, 1945.

9. Livingston, S.; Kajdi, L., and Bridge, E. M.: The Use of Benzedrine and Dexedrine Sulfate in the Treatment of Epilepsy, J. Pediat. **32**:490, 1948.

10. Bradley, C.: Benzedrine and Dexedrine in the Treatment of Children's Behavior Disorders, Pediatrics **5**:24, 1950.

11. Williams, R. H., and others: Obesity and Its Treatment, with Particular Reference to the Use of Anorexigenic Compounds, Ann. Int. Med. **29**:510, 1948.

use of the amphetamines has resulted in their availability in numerous forms. However, the prescription label on these forms carries no warning concerning the toxicity of the drug. A number of the preparations contain phenobarbital in addition to the dextroamphetamine. However, the quantity of phenobarbital is apparently not adequate to overcome the toxic central-nervous-system effects, as the above case illustrates.

The subject of the report ingested at least 40 mg. of dextroamphetamine sulfate and 60 mg. of phenobarbital. When these amounts are calculated in relation to various constants, the child ingested 2.9 mg. of dextroamphetamine sulfate per kilogram of body weight, or 70.2 mg. per square meter of body surface, and 4.3 mg. of phenobarbital per kilogram of body weight, or 103.4 mg. per square meter of body surface. The toxic symptoms present were due to the known central-nervous-system effect of the dextroamphetamine; they began within one-half hour of ingestion of the drug and were progressive in nature until sedation was initiated five and one-quarter hours after ingestion of the drug. Mydriasis and flushing of the face, the adrenergic symptoms that were noted at the time of admission to the hospital, disappeared within 24 hours. The individual symptomatic responses to the central-nervous-system stimulation disappeared at varying times, as witnessed by the hyperactivity disappearing in two days, the euphoria, in seven days, and the ataxia, in eight days. Since the euphoria and ataxia were not materially affected by the barbiturates that were given, we cannot be certain that these late symptoms were not the result of an atypical phenobarbital reaction.

The treatment of this case of dextroamphetamine poisoning was symptomatic. Gastric lavage and dilution of the poison were accomplished with isotonic saline. Since amphetamine is destroyed slowly in the body, and the kidney is the main pathway of excretion, intravenously administered fluids were used to increase the urinary volume. Barbiturates were used to reduce the cerebral stimulation and the resultant hyperactivity. The knowledge that a poststimulation depression could occur following the use of any central-nervous-system stimulant tempered our use of sedatives.

SUMMARY

A successfully treated case of acute dextroamphetamine sulfate poisoning has been presented. The literature concerning amphetamine poisoning and the pharmacology of the amphetamines has been briefly reviewed. It is suggested that dextrorotatory forms of amphetamine carry a warning concerning the potential toxicity of the drug.

CONGENITAL ATRESIA OF THE BILIARY SYSTEM

Delayed Development of Correctability

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THE EARLIEST report of atresia of the biliary system in newborn children offered no suggestion of treatment and relegated this condition to the status of a congenital anomaly inevitably terminating in death.[1] Twenty-four years later, however, Holmes, after careful study of the pathologic material, suggested that in some instances surgical intervention might have established a successful connection between the liver and the intestinal tract.[2] This opinion was brilliantly confirmed by Ladd [3] and later by Donovan,[4] so that early operation is now generally accepted as the proper treatment.

However, these authors and others have reported a substantial proportion of cases in patients in whom exploration reveals a condition of the biliary system deemed to be uncorrectable. Moore, for example, recently reported a total of 135 cases, including 31 of his own.[5] In 77% of these cases the biliary system was absent or had not passed the stage of solid cords in their embryonic development. Such cases are generally classified as uncorrectable. Our case seemed to fall into this category.

REPORT OF CASE

R. J., a 4-month-old white boy baby, was admitted to the Jewish Sanitarium and Hospital for Chronic Diseases with a diagnosis of congenital atresia of the bile ducts and absence of the gall bladder. Family history was not remarkable. The infant was born at full term, weighing 6 lb. 12 oz. (2,610 gm.), and appeared normal except for a telangiectasis of the nose. At 5 weeks of age jaundice was noted, the urine became a deep yellow-brown, and the stools turned light yellow in color. He was admitted to St. Luke's Hospital. At this time the child was afebrile and appeared moderately well nourished and developed for his age. The liver was palpated one and one-half fingerbreadths below the right costal margin. He was transferred to

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Read in part before the Brooklyn Academy of Pediatrics.

From the Jewish Sanitarium and Hospital for Chronic Diseases, Brooklyn, and St. Luke's Hospital, New York.

1. Thompson, J.: On Congenital Obliteration of the Bile-Ducts, Edinburgh M. J. **37**:523, 604, and 724, 1891-1892.

2. Holmes, J. B.: Congenital Obliteration of the Bile Ducts: Diagnosis and Suggestions for Treatment, Am. J. Dis. Child. **11**:405, 1916.

3. Ladd, W. E.: Congenital Atresia and Stenosis of the Bile Ducts, J. A. M. A. **9**:1082, 1928.

4. Donovan, E. J.: Congenital Atresia of the Bile Ducts, Ann. Surg. **106**:737, 1937.

5. Moore, T. C.: Congenital Atresia of the Extrahepatic Bile Ducts, Surg., Gynec., & Obst. **96**:215, 1953.

TABLE 1.—*Laboratory Findings for Infant R. J.*

	Protein Metabolism (Chemical Studies)								
	Normal Values	Jan.	Feb.	March	April	July	Sept.	Oct.	Dec.
Total protein, gm./100 cc.	5.5-7.5	7.5	6.8	7.48	7.74	7.9	7.4	7.1	7.66
Albumin, gm./100 cc.	3.5-5.5	5.3	3.2	3.45	3.45	2.6	2.8	2.5	1.77
Globulin, gm./100 cc.	1.5-3.0	2.2	3.6	4.03	4.29	5.2	4.6	4.6	5.89
A/G ratio	1.5	2.4	0.9	0.85	0.8	0.5	0.6	0.55	0.3

TABLE 2.—*Laboratory Findings for Infant R. J.*

	Protein Metabolism (Electrophoretic Studies)				
	Normal Values	Feb.	July	Sept.	Dec.
Total protein, gm./100 cc.	6.5-8.5	6.79	7.90	7.38	7.64
Albumin, gm./100 cc.	4-5	2.35	1.78	1.78	1.19
Globulin, gm./100 cc.	2.5-3.5	4.44	6.12	5.60	6.45
Alpha 1, gm./100 cc.	0.3-0.5	0.48	.72	.53	.47
Alpha 2, gm./100 cc.	0.5-0.7	0.93	1.26	.78	.55
Beta, gm./100 cc.	0.8-1.0	1.46	1.95	1.12	1.82
Gamma, gm./100 cc.	0.8-1.2	1.58	3.10	3.18	3.61
A/G ratio	.....	0.53	0.29	0.32	0.18

TABLE 3.—*Laboratory Findings for Infant R. J.*

	Flocculation Tests						
	Babies Hospital, Jan.	Jewish Sanitarium and Hospital for Chronic Diseases					
		Feb.	March	April	July	Sept.	Dec.
Thymol turbidity	Normal	...	2.5-3.7	8.3	10.2	7.7	8.2
Zinc SO_4 turbidity	4.9	...	.....	13.6	....	...	...
Cephalin flocculation	Normal	2+	3+	4+	4+	4+	4+

TABLE 4.—*Laboratory Findings for Infant R. J.*

	Biliary Pigments						
	Babies Hospital, Jan.	Jewish Sanitarium and Hospital for Chronic Diseases					
		Feb.	March	April	July	Sept.	Dec.
Icterus index	....	39.1	48.5	48.5	40.0	40.8	40
Bilirubin	17.4	....	....	11.9	....	7.2	..
Direct	7.3	....	....	....	....	2.7	..
Indirect	10.	....	....	....	....	4.5	..

TABLE 5.—*Laboratory Findings for Infant R. J.*

	Lipid Metabolism				
	Babies Hospital, Jan.	Jewish Sanitarium and Hospital for Chronic Diseases			
		March	June	Oct.	Nov.
Total lipids, mg./100 cc.	...	...	550	260	..
Cholesterol lipids, mg./100 cc.	315	195	...	74	91
Cholesterol esters					
Amount, gm./100 cc.	110	69	...	31	65
% of total cholesterol	34.9	28.3	...	42	71

the Babies Hospital, where at the age of 3 months an exploratory operation was performed by one of us (E. D.). Complete atresia of the extrahepatic biliary system was found. The gall bladder was absent. The condition was deemed uncorrectable, and the abdomen was closed.

One month later, when admitted to the Jewish Sanitarium and Hospital for Chronic Diseases, the infant was markedly underdeveloped and jaundiced. The abdomen was distended; the liver was palpable 4 to 6 cm. below the right costal margin, and the spleen edge was 2 cm. below the left costal margin.

The course in the hospital was featured by frequent bouts of fever, usually in conjunction with upper respiratory infection which responded quickly to antibiotic or chemotherapeutic agents. In addition, there were a number of bouts of diarrhea associated with nausea and

Fig. 1.—Distended gall bladder in approximately normal location. Remains of fibrous adhesions which prior to sharp dissection had covered the gall bladder and upper surface of the liver and which had extended to the pylorus of the stomach and the superior portion of the duodenum.

vomiting, controlled by restriction of diet. There were also frequent periods of lethargy. The stools were putty-like in consistency, clay-colored with absent bile pigment. The urine was bile-stained.

While in the beginning the size of the liver increased somewhat, it regressed in size during the last few months. Moreover, increasing ascites made it more difficult to delineate the borders of both the liver and the spleen. Terminally, the patient appeared like a scrawny infant built around a huge dome-like abdomen with visible compensatory collateral circulation.

The child was kept on a low fat-high protein diet, with adequate carbohydrate supplement. Although he ate quite well, the child's emaciation steadily grew worse. Several paracenteses

were performed, 700 cc. of abdominal fluid being drained off on one occasion. Because of his anemia several transfusions were given. Despite these measures, the child gradually declined and died at 18 months of age with the signs and symptoms of hepatic insufficiency and marked inanition.

The laboratory findings at all three hospitals are summarized in Tables 1, 2, 3, 4, and 5. Other findings were as follows: The urine was positive for bile and albumin, and occasionally blood appeared; there was a faint trace of urobilinogen several times. The stools showed no bile pigments. The blood calcium was 8 mg. per 100 cc.; phosphorus, 3.2 mg. per 100 cc. Vitamin A- and carotene-tolerance tests showed a low flat curve. The blood glucose value was 74 mg. per 100 cc. Examination of the abdominal fluid obtained by paracentesis showed a

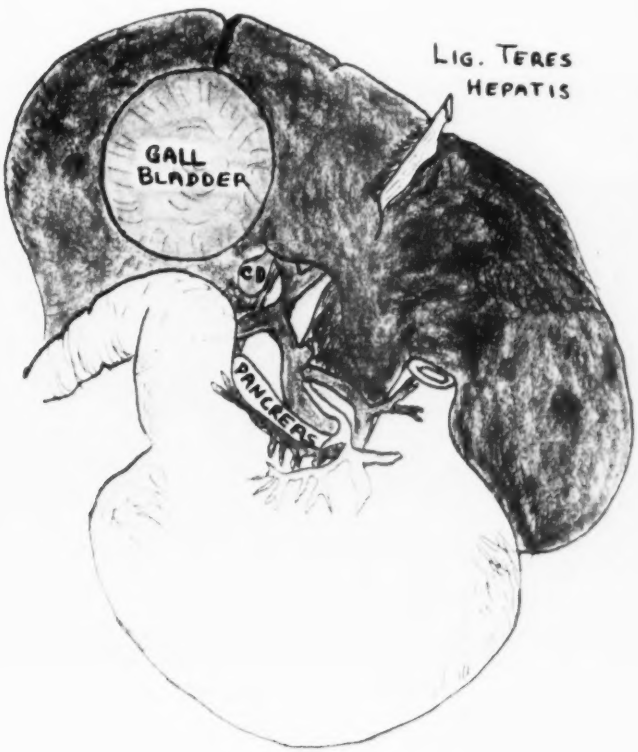

Fig. 2.—Schematic representation of findings at autopsy. Hepatic artery and portal vein to the right. At the left common duct (*C.D.*) terminates as a blind sac. The cystic duct is absent.

total protein of 1.11 gm. per 100 cc., with a value for albumin of 0.31 gm. and for globulin of 0.80 gm. per 100 cc. Acid and alkaline phosphatase values were increased to as high as 7.8 and 21.9 King and Armstrong units, respectively. The erythrocyte sedimentation rate was 32 mm. in one hour. The hemoglobin value dropped to as low as 7.4 gm. per 100 cc. and was maintained only by repeated transfusions. The white blood cell count was normal except for an occasional rise of the value for eosinophiles to 12%. The urea nitrogen and potassium were normal. The results of the Mazzini test were negative. X-rays of the skull and long bones including the epiphyseal development were reported as normal until late in the course of the illness, when considerable decalcification of the long bones was noted.

Postmortem findings in the area of the liver were as follows: The weight of the liver was 440 gm. The liver surface was uneven and nodular. The anterior surface was covered by a thick fibrotic scar probably resulting from the early operation. When this was dissected away, a large gall-bladder-like structure was found to be present (Fig. 1). This organ was markedly distended, measured about 7 cm. in diameter, and was filled with 35 cc. of dark green viscid bile. The mucosa was thickened and ulcerated. The wall measured up to 2.5 mm. in thickness. There was no connection between the gall bladder and the extrahepatic bile ducts. However, a thin probe found a direct connection between the gall bladder and a dilated duct in the liver parenchyma near the porta hepatis. The condition of the rest of the extrahepatic biliary system is illustrated in Fig. 2. The common duct was missing except for a markedly distended stump which measured 3 cm. in diameter and was filled with bile. Both hepatic ducts could be followed into the liver. The liver showed an increased resistance when cut. It had a green-brown discoloration. The liver parenchyma was traversed by numerous thin and thick fibrous strands. The intrahepatic bile ducts, particularly of the right lobe, were markedly distended and in some

Fig. 3.—Cut section of the liver demonstrating marked enlargement of the intrahepatic ducts which frequently contain biliary concretions. There is extensive fibrosis of the hepatic parenchyma with distortion of the normal architecture.

areas measured up to 1.2 cm. in diameter (Fig. 3). They contained dark green tenacious bile as well as numerous mulberry-shaped black pigment stones. The anatomical diagnosis was as follows: congenital atresia of the cystic duct and of the common duct; severe biliary cirrhosis; marked dilatation of the gall bladder; hepatocystic duct connecting the gall bladder directly with the liver; marked dilatation of the intrahepatic ducts with formation of intraductal gallstones; severe icterus; fibrous adhesions connecting the liver with the pylorus and the superior portion of the duodenum; ascites; moderate bilateral hydrothorax.

COMMENT

The discovery of biliary tract structures a few months after experienced and meticulous operative exploration had revealed none served to focus our attention on those other cases which were considered uncorrectable. We searched the

TABLE 6.—*Late Development of Correctability (14 Cases) 1st Exploration*

Author	Case No.	1st Exploration: Age, Mo.	1st Exploration: Condition of Gall Bladder and Bile Ducts	Autopsy: Age, Mo.	Autopsy: Condition of Gall Bladder and Bile Ducts
Kanof, Donovan, and Berner....	..	3	Absent	18	Markedly distended "gall bladder"; 2 hepatic ducts and stump of common duct
Moore [5]	4		No biliary structures found	12	Markedly dilated hepatic duct found in lesser peritoneal cavity behind gastrohepatic ligament
Donovan [4]	7	2	Gall bladder small and colorless, extrahepatic ducts appearing as fibrous cords	3-1	Gall bladder measured 2 cm. in length and contained 0.5 cc. thin colorless fluid; leading from gall bladder was narrow duct which could be traced for only 2.5 cm. and ended blindly; common duct and hepatic ducts not present
	14	1	Gall bladder and bile ducts undeveloped	2	Undeveloped gall bladder with anomalous insertion of cystic duct into right hepatic duct; complete obliteration of common duct
Laboe [6a]	..	3	Undersurface of liver explored by direct vision; in gall bladder fissure cystic-appearing mass found which seemed to be of rudimentary gall bladder; no ducts visible	5	Gall bladder represented by small sac about 4 mm. by 15 mm. containing no bile; cystic duct could not be demonstrated; lying just to left of gall bladder was cystic mass about 1 cm. in diameter; this found to be filled with bile; no outlet could be demonstrated; beneath this and extending into right and left lobes of liver were 2 dilated bile-filled ducts which met at and were attached to the cyst; no communication found between them; no evidence of common bile duct
Ahrens, Harris, and MacMahon [6d]	1	13	No evidence of gall bladder; no bile ducts	30	Gall bladder 5 cm. by 1 cm., distended with dark-green viscid material and in normal position; common duct 1 mm. in diameter, patent, and green-stained; right hepatic duct less than 1 mm. in diameter, patent, and bile-stained; left hepatic duct consisted entirely of fibrous tissue and had no lumen; it was not bile-stained
	3	11	Gall bladder small, white, empty, and thick-walled; all ducts white and cordlike	30	Gall bladder 3 cm. by 1 cm. and contained bile; cystic duct bile-stained and patent for 1 cm., then became a thick fibrous cord which extended to ampulla of Vater; hepatic ducts not identified
Leyva and Madigan [6f]	..		Congenital anomaly not seen	1	Atresia of lower end of hepatic duct with large cystic dilatation of duct proximal to obstruction
Woolley [6g]			Normal components of gall bladder could not be found	1	Normal biliary structures
Finlayson [6i]	..	11	Gall bladder small, white, and empty, with thick walls; duct white in color and felt like hard cords; considered inoperable	28	Gall bladder 3 cm. by 1 cm., with bile-stained contents; from neck of gall bladder a duct was pervious and bile-stained for ½ in. (1.3 cm.), after which it was represented by an impervious cord the size of thick catgut
Ladd [3]	136370		No extrahepatic ducts	..	Atresia of the common duct which could have been anastomosed to the duodenum; it was operable
Freeman and Sexton [6j]	5	2	Small atrophic gall bladder found which contained small amount of mucus; complete absence of extrahepatic biliary ducts	8	No bile ducts on cut section of parenchyma of liver, but in vicinity of hilum there were a number of duct structures with blind endings
McCarty and Pence [6l]	..	1½	Region of the hepatoduodenal ligament thoroughly dissected and explored; no hepatic or common bile duct whatever found; gall bladder 13 mm. long and 8 mm. wide found; no duct leading from this gall bladder found; hepatoduodenal fistula established	8	When this fistula was opened, a sinus tract 3.5 cm. by 0.8 to 1.2 cm. was exposed; into this tract opened several bile ducts; neither these ducts nor those elsewhere in the liver were dilated
Stolkind [6k]	19	1½	Obliteration of bile ducts	2½	Gall bladder small, partly filled with mucus; both hepatic ducts not patent, but common bile duct seemed patent

literature for cases resembling ours, cases in which an early exploratory operation had revealed an uncorrectable condition of the biliary tract, but in which postmortem examination later revealed the presence of some degree of duct or gallbladder development. We eliminated cases in which death followed exploration so soon that the difference in findings might have been considered more logically as due to insufficient inspection at the first procedure. Fourteen cases [6] (Table 6) were found in which it appeared that there had been an actual anatomic change between the time of operation and the autopsy examination.

These cases, as well as ours, seem to suggest that the biliary system may continue to develop after birth. Such development may come about in two ways. In the first place, the development of patent ducts may be due to the pressure of bile forming in the liver and, deprived of its normal pathways of egress, dilating and protruding the normally intrahepatic duct system. A recent study has emphasized the size to which intrahepatic liver ducts may develop when the normal structures are absent,[6a] and in our case, also, tremendously dilated intrahepatic ducts were described. The gall bladder in our patient filled by an opening into the liver tissue, and, not being connected to the extrahepatic bile duct, it may have been the extreme result of such bile pressure. Laboe also postulated this possibility in his case.[6e]

In other cases, there may be simply delayed embryonic development of the normal structures. This process could have accounted for the discovery of two hepatic ducts and the stump of a common duct in our patient at autopsy. Such delay is seen in the development of other organs. In addition to explaining the course of events in our patient and those in the cases enumerated in Table 6, this hypothesis may also serve to explain the occasional report of an instance in which early exploration revealed absence of biliary structures, but in which the child nevertheless made a complete recovery.[7]

The normal protein values in the presence of an icteric index of 40 and a bilirubin value of 7.3 substantiated the diagnosis of an unmodified obstructive jaundice early. The drop in the albumin value and the increasing values for the globulins indicated increasing failure of the hepatic parenchyma. The increase

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6. (*a*) Ladd.[3] (*b*) Donovan.[4] (*c*) Moore.[5] (*d*) Ahrens, E. H., Jr.; Harris, R. C., and MacMahon, H. E.: Atresia of the Intrahepatic Bile Ducts, Pediatrics **8**:628, 1951. (*e*) Laboe, E. W.: Congenital Absence of Bile Ducts, with Report of Case, J. Indiana M. A. **27**:373, 1934. (*f*) Leyva, F. R., and Madigan, H. S.: Congenital Biliary Atresia, Clin. Proc. Child. Hosp. **4**:309, 1948. (*g*) Woolley, P. V.: Clinical Conference: Congenital Obliteration of Bile Ducts, J. Pediat. **33**:509, 1948. (*h*) Finlayson, C.: Congenital Obliteration of the Bile Ducts in a Child Who Lived for 3 Years and 3 Months, Arch. Dis. Childhood **12**:153, 1937. (*i*) Freeman, G. C., and Sexton, H. M.: Biliary Atresia: Review of 7 Cases, Proc. Staff Meet. Clin., Honolulu, **15**:71, 1949. (*j*) McCarry, F., and Pence, L. C.: Surgical Relief of External Biliary Duct Atresia, West. J. Surg. **58**:714, 1950. (*k*) Stolkind, E.: Congenital Abnormalities of the Gall-Bladder and Extrahepatic Ducts: Review of 245 Reported Cases with Reports of 31 Unpublished Cases, Brit. J. Child. **36**:115, 182, and 295, 1939.

7. Footnotes 4 and 6*d*. Amberg, S., and Logan, G. B.: Diseases of the Liver and Biliary Tract, in Brenneman's Practice of Pediatrics, edited by I. McQuarrie, Hagerstown, Md., W. F. Prior Company, Inc., 1948, Vol. 3, Chap. 11. Hsia, D. Y. Y.; Patterson, P.; Allen, F. H., Jr.; Diamond, L. K., and Gellis, S. S.: Prolonged Obstructive Jaundice in Infancy: I: A General Survey of 156 Cases, Pediatrics **10**:243, 1952.

in the thymol turbidity values parallels the increase in the beta globulins, while the rising cephalin flocculation is a fairly good index of the rise in the gamma globulin.

CONCLUSIONS

It would appear from our case and the others reported that in a patient with biliary atresia early operation is still indicated. However, in patients in whom early exploration reveals a seemingly hopeless state of affairs, reexamination at a later date should not be discouraged.

Deterioration of the protein metabolism seemed to follow the downhill course of this patient. Thymol turbidity and cephalin flocculation tests seem to mirror, quite accurately, the course of the beta and gamma globulin in the blood.

Dr. Bruno Volk helped with description and evaluation of the pathological specimens.

CHONDRODYSPLASIA (ACHONDROPLASIA) IN ONE OF DIZYGOTIC TWINS

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THE TERM "chondrodysplasia" is used to denote a condition characterized by faulty development of cartilage and growth of bone in the ossification centers of bones of nonmembranous origin, while the periosteal formation of bone takes place at a normal or a slightly increased rate. The disturbance involves chiefly longitudinal growth resulting in widening of the epiphyses, irregularity of the epiphyseal lines, and short thickened bones as seen in the roentgenograms.[1] Clinically the condition manifests itself in typical cases by shortness of stature. This is due to shortness of the legs, but the trunk is of normal length. The arms rarely extend beyond the trochanters. The hands are broad, short, and often trident. The head appears large with sunken nasal bridge and prominent forehead and lower jaw.

This condition is often called "achondroplasia." The prefix *a*, however, means "no" and the word "achondroplasia" would indicate a condition in which formation of cartilage does not take place (*chondros*: cartilage; *plasia*: formation). This is not the case in the described condition, and the word "chondrodysplasia," meaning disturbed (*dys*: disturbed) formation of cartilage, would seem to be more appropriate. The term "chondrodystrophy" also has been used. This implies that disturbed nutrition of cartilage is the cause. As the cause of the condition still is unknown, the term "chondrodystrophy" would seem to be inappropriate.

Chondrodysplasia usually appears in isolated cases, but in some instances a definite familial tendency can be found. The ratio between the former and the latter is about 6:1. According to Mørch,[2] who studied 108 cases of chondrodysplasia in Denmark, the occurrence of the disorder in families can be explained genetically on the basis of a dominant mode of transmission.

The incidence of chondrodysplasia is said to be about once in every 10,000 to 12,000 births. Dizygotic twins occur once in about every 135 births, and the two together, that is, chondrodysplasia in a dizygotic twin, would be encountered once in about every 1,350,000 to 1,620,000 births. According to Mørch, chondrodysplasia in one of dizygotic twins has been reported 10 times in the literature. In seven cases

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1. Pugh, D. B.: Achondroplasia and Osteochondrodystrophy, in Golden, R.: Diagnostic Roentgenology, Baltimore, The Williams & Wilkins Company, 1948, vol. 2, pp. 455-463.

2. Mørch, E. T.: Chondrodystrophic Dwarfs in Denmark. (Supplemented with investigations from Sweden and Norway) with special reference to the inheritance of chondrocystrophy. Copenhagen, Ejnar Munksgaard Forlag, 1941, 200 pp.

the twins were of different sex and thus with certainty dizygotic.[3] In one of these seven cases the condition was diagnosed as atypical achondroplasia. All measurements were normal except for a slightly shorter femur than normal. Roentgenograms showed delayed epiphyseal growth and flattening of the thoracic vertebrae.[3e] In another case it was stated that the twin had an "achondroplastic appearence" only.[4] In two of the remaining three pairs of twins the children were of the same sex. It was assumed that they were dizygotic in one case [5] and monozygotic in another.[6] In the third case the sex of the unaffected twin was not known.[2]

The following report is of a Mayo Clinic case in which chondrodysplasia occurred in one of dizygotic twins, the diagnosis being made at the time of birth.

REPORT OF CASE

The mother was 32 years 2 months of age and had had five children previously, two girls and three boys. She had not had any miscarriages, but the first child, a boy born in 1942, was premature (birth weight, 2,390 gm.; length, 46 cm.). Except for the second child, each child had had a thorough examination at birth and regular examinations during the first years of life. No abnormalities had been found.

During the last pregnancy the mother had felt well. She had noticed some dark-colored or red urine in the sixth month. However, the results of urinalysis were negative at each prepartal examination. Twin pregnancy was diagnosed on examination by roentgenogram on April 26,

Measurements for Chondrodysplastic Twin and His Normal Brother

Age	Weight, Gm.	Height, Cm.	Sitting Height, Cm.	Circumference, Cm.		Leg *	Arm †
				Head	Chest		
At birth	2,850 (2,620 ‡)	46.5 (47)	....	34.5 (32.0)	30 (30)	....	....
3 mo.	4,016 (3,768)	50.8 (54)	35.6 (34.0)	40.6 (37.4)	35.6 (38.7)	15.8 (22.9)	11.5 (15.2)
6 mo.	6,124 (7,252)	59.7 (67)	40.6 (40.3)	45.4 (41.9)	37.5 (44)	20.3 (32)	13.3 (17.2)

* The leg is measured from the ventral iliac spine to the malleolus of the tibia.
† The arm is measured from acromion to the radial condyle.
‡ Measurements in parentheses are those for the normal twin (T [II] M).

1952. Anti-Rh conglutinin titer was 0 on April 5, and her blood was of the O,N group. Serologic reactions were negative. Onset of labor took place May 2, which was 10 weeks before the expected termination of pregnancy. After one hour the first twin, T(I)M, was delivered spontaneously. The child cried well at once. It was noticed that the arms and legs appeared shorter than normal. After version the second twin, T(II)M, was extracted half an hour later. This child appeared to be normal.

The placenta was bilobar. Pathologic examination revealed two amnions and two chorions. It was concluded that the two placentas had fused. Typing of the blood showed the first twin to be O,N, Rh$_0$ and the second one O,MN, Rh$_0$.

The head of the first twin appeared to be unusually large and the extremities unusually short (Fig. 1). The remainder of the physical examination did not reveal any further abnormality. The measurements are given in the Table.

3. (*a*) Mørch.[2] (*b*) Parhon, C., and Schunda, A.: Nouvelle contribution a l'étude de l'achondroplasie, Nouv. iconog. de la Salpêtrière, Par., **26**:185-201, 1913. (*c*) Pritchard, E.: An Atypical Case of Achondroplasia in a Twin, Brit. J. Child. Dis. **25**:101-106, 1928. (*d*) Peralta, Ramos, A. G., Jr., and Murtagh, J. J.: Acondroplasia en un solo gemelar, Dia méd. **10**:764-769, 1938. (*e*) Rischbieth, H., and Barrington, A.: Dwarfism, in Treasury of Human Inheritance, London, Dulau and Co., Limited, 1912, vol. 1, pp. 355-573.

4. Hutchison, R.: Achondroplasia in a Twin, Proc. Roy. Soc. Med. **3**:41, 1910.

5. Warner, A.: An Achondroplastic Twin, Brit. M. J. **2**:983, 1928.

6. Benjamin, E. L., and Brookner, A.: Achondroplasia in a Twin, J. Pediat. **4**:352-355, 1934.

Fig. 1.—Photograph taken at birth. T(I)M at right, T(II)M at left. Note the short extremities and large head of T(I)M as compared with his normal brother, T(II)M.

Fig. 2.—Roentgenograms taken at birth. (*a*) T(I)M. Shortness of the long bones and irregularity of the metaphyses are present. (*b*) Skeletal development of twin brother, T(II)M, is essentially normal.

Physical examination showed the second twin to be normal except for the testes, which could be palpated in the inguinal canal. They could be expressed into the scrotum at this time. The appearance was normal (Fig. 1).

Roentgenograms of the first twin showed considerable shortening of the shafts of the long bones with irregularities at the metaphyseal ends of the bones, some thickening of the midshaft, and some deformity (Fig. 2*a*). The roentgenograms of the second twin were essentially normal (Fig. 2*b*).

Both twins were artificially fed and remained in the hospital for six days after birth. The course of the hospital stay was uneventful.

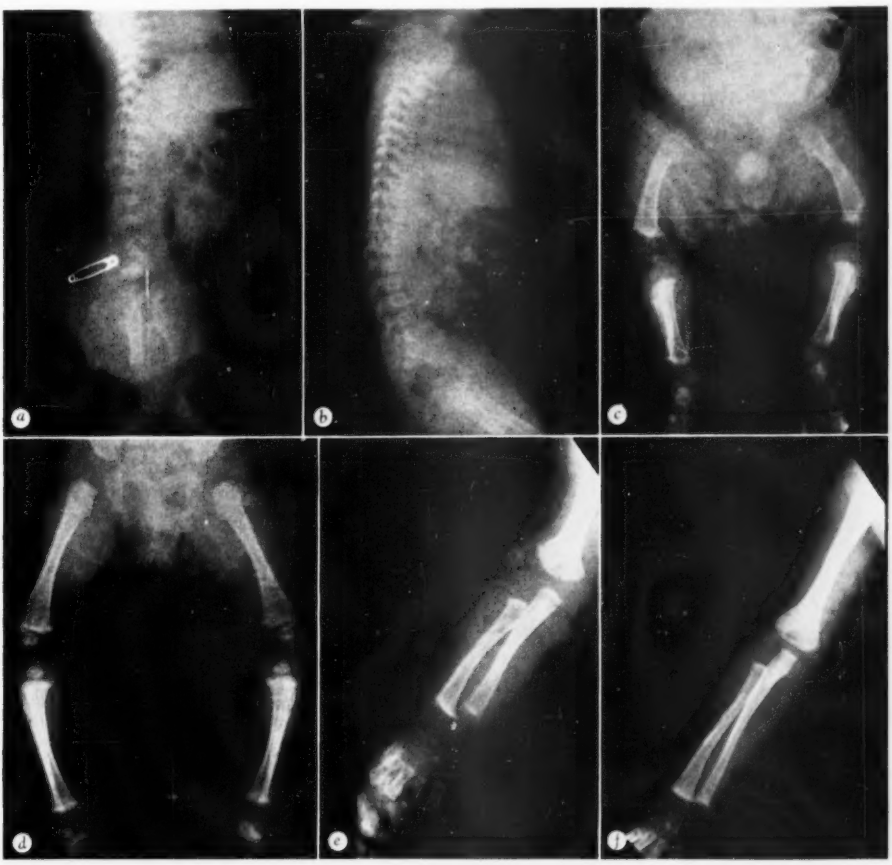

Fig. 3.—(*a*) and (*b*) spinal columns of dizygotic twin boys at 3 months of age. Note flattening of verebral bodies, increased thickness of intervertebral disks, and horizontal position of sacrum in (*a*), T(I)M as compared to those of normal brother in (*b*), T(II)M. (*c*) and (*d*) lower extremities of same infants at 3 months of age. Shortness, thickening, and irregular metaphyses may be noted in (*c*), T(I)M. Note absence of distal femur and proximal tibial ossification center as compared with that of normal brother, T(II)M, in (*d*), (*e*), and (*f*). Upper extremities of same infants at 3 months of age. Shortness and thickening of long bones of T(I)M in (*e*) are conspicuous in comparison with upper extremities of normal brother, T(II)M, in (*f*).

After discharge from the hospital the twins were examined clinically every month. At the age of 3 months the first twin could not raise his head and was not smiling or cooing. The patellar reflexes were elicited with difficulty. The head appeared large, but bulging of the fontanels was not present. Roentgenograms at this time revealed nothing pathologic in the lungs. The skull

was within normal limits. Roentgenograms of the skeleton showed deformities which involved almost all bones and were due to faulty endochondral growth. The shafts of the long bones were short and thick, with irregular and deformed metaphyses. The epiphyses were absent at the knees and wrists. The metacarpals were short and thick, as were the metatarsals. The spinal column showed some thoracolumbar kyphosis; the vertebral bodies were flattened, and the thickness of the intervertebral disks was increased (Fig. 3*a*, *c* and *e*). The measurements are given in the Table.

The second twin had good control of his head and had been smiling and cooing since the first month of life. At 8 weeks of age he was admitted to the hospital because of a mucous plug in the airways associated with a cold. He was discharged the next day. The mother stated that he always had a "barking" cough even when he did not have a cold. The results of physical examination were negative, and nothing abnormal was evident on the roentgenograms of the thorax, head, spinal column, and extremities (Fig. 3*b*, *d*, and *f* and Table).

The twins were seen again at 6 months of age. Up to the age of 5 months the first twin had not been able to raise his head and had not smiled or cooed. He preferred to lie on the left side with the back arched and the head thrown back. A gibbous deformity of the back in the

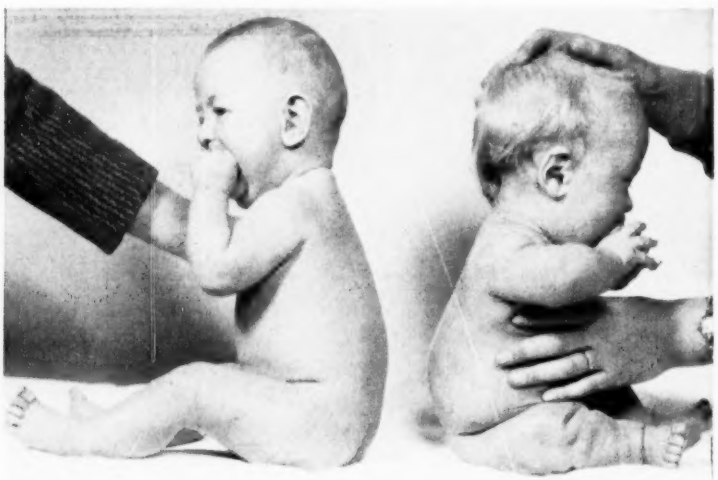

Fig. 4.—Dizygotic twin boys at 6 months of age. Large head, short extremities, and thoracolumbar gibbus are exhibited by T(1)M (right).

upper lumbar region had become evident at 4 months of age. At 6 months of age, however, he was able to move his head and raise it just off the examination table. When held in the upright position, he could control his head fairly well. The arching of the back was no longer as prominent, and the head was held in a normal position. The gibbus was still marked (Fig. 4). Two lower central incisors had erupted. He was now smiling and cooing, and the mother felt that he had a much pleasanter disposition than his normal brother. Roentgenograms of the spinal column revealed angulation with a tendency toward gibbus and sharp angulation of the sacrum with posterior prominence of the tip of the sacrum and coccyx. There was continued failure of endochondral growth with resultant deformity and shortening of the shafts of the long bones (Fig. 5 and Table).

Physical examination of the second twin did not disclose any abnormality. His development was normal for his age (Table).

Evidence of similar disturbances of skeletal growth occurring in this family was not discovered. The mother and father were both healthy and did not show any gross skeletal abnormalities. As previously noted, all siblings were normal. All four grandparents came from Norway, and none of these, or any of the granduncles, grandaunts, uncles, or aunts had a history of skeletal abnormalities (Fig. 6).

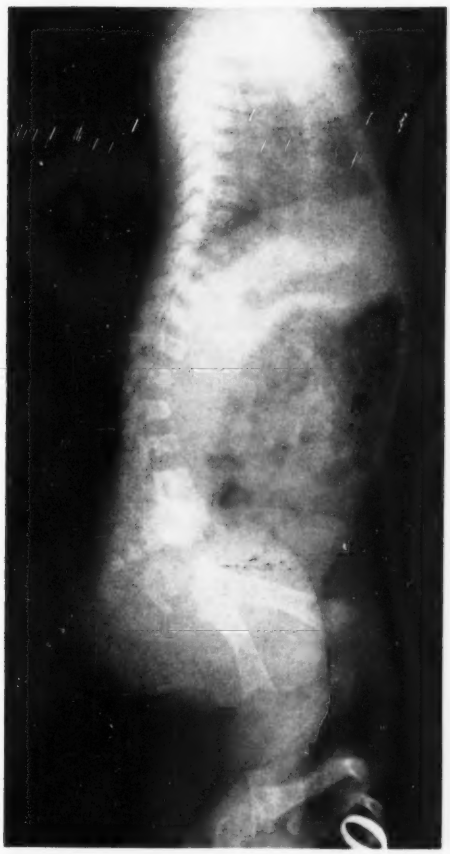

Fig. 5.—Spinal column of T(I)M at 6 months of age. Evidence of thoracolumbar gibbus is present.

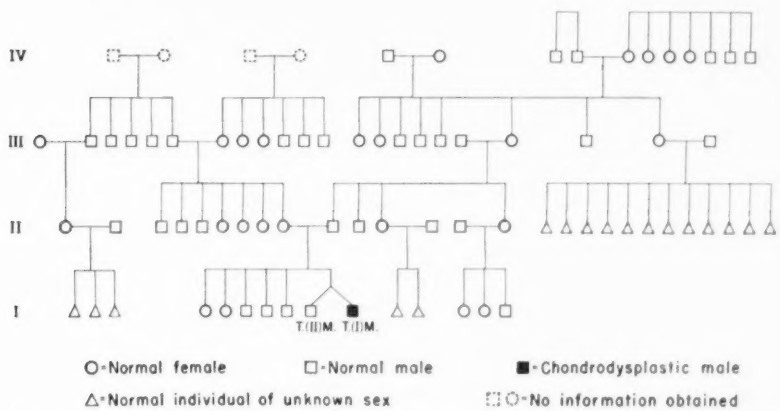

Fig. 6.—Pedigree showing most of four generations. Members of the fourth generation came from Norway or were living there. The other generations are living in the United States, almost all members being settled in Minnesota or the Dakotas.

COMMENT

Chondrodysplasia occurring in one of dizygotic twins is of special interest in relation to the many theories about the cause of the disturbance. Some writers have assumed disturbances of the maternal organism or, more specifically, disturbances of intrauterine conditions to be the cause of chondrodysplasia. In the case which we have presented, in which the two placentas were fused in the center, the environmental conditions of the two fetuses would presumably have been similar. It would seem that disturbances of the maternal organism or the intrauterine conditions probably were not the cause of chondrodysplasia in this case. A change in the genetic pattern of one of the twins seems to be the most likely cause. As disturbances of similar character were not found in the family, it must be assumed that the change was due to mutation. This can be an assumption only, because a more thorough investigation of the members of the family would be necessary to give better support for such a theory. For practical reasons it has not been possible to carry out such an investigation.

Our case is one of severe chondrodysplasia. Most of the bones of the skeleton are involved, and the spinal column shows marked flattening of the vertebral bodies. It is interesting that the intervertebral disks are increased in thickness. The sitting height of the chondrodysplastic twin is therefore the same or even greater than that of the normal brother.

Slow development is reported to be characteristic of chondrodysplastic infants during the first months of life, but development during the second half of the first year almost seems to be accelerated until by 1 to 1½ years of age the mental and motor development is within the range of normal.[7] The mortality among chondrodysplastic infants is above the average for normal infants during the first year of life, but after this there is no difference.

7. Caffey, J.: Achondroplasia, in McQuarrie, I.: Brennemann's Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1948, vol. 4, Chap. 28, pp. 1-22.

ABSENT ABDOMINAL MUSCULATURE, GENITOURINARY ANOMALIES, AND DEFICIENCY IN PELVIC AUTONOMIC NERVOUS SYSTEM

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THE SYNDROME of absence of anterior abdominal musculature and coexisting genitourinary abnormalities is being presented at this time because absence of ganglion cells in the bladder was found in two of our three cases. The suggestion of this as a factor in the origin of megaloureter not associated with absent anterior abdominal musculature has been made by Swenson.[1] Two of our three cases were also interesting because there was definite organic vesical neck obstruction.

REPORT OF CASES

CASE 1.—J. G. (No. 244226), a 5-month-old white boy, was first seen at the Bronx Hospital in November, 1951, in an episode of acute laryngotracheobronchitis associated with bronchopneumonia. The absence of anterior abdominal musculature had been noted at birth. Study of the urinary system at another hospital shortly after birth was unsuccessful, but the nonprotein nitrogen value was normal at that time. Examination on admission to this hospital revealed the absence of the anterior abdominal musculature and resultant bulging of the flanks, with palpable abdominal masses thought to be the liver, the spleen, and both kidneys. The intestinal pattern could at times be discerned through the abdominal wall; also noticeable were phimosis, bilateral inguinal undescended testicles, and an undeveloped scrotum. Cystoscopy under general anesthesia revealed multiple anterior urethral strictures which had to be dilated before cystography could be performed. The cystogram demonstrated marked dilatation of the urinary bladder, with its superior border at the second lumbar level and a concavity at the urethrovesical neck suggestive of outlet obstruction.

Intravenous pyelography showed tremendous dilatation of both ureters, with good dye excretion bilaterally. Findings on a roentgenogram after a barium meal were normal; with a barium enema redundancy of the colon was shown. Laboratory studies during this admission showed moderate hypochromic anemia, a blood urea nitrogen value of 12.4 mg. per 100 cc., a cloudy urine with 8 to 10 white blood cells per high power field, 4 to 8 red blood cells per high power field, no casts, a trace of albumin, and specific gravity up to 1.030.

The patient was discharged and followed in the clinic and did well until 14 months of age, when he was readmitted with a history of hematuria of 24 hours' duration and a temperature of 103 F. associated with an upper respiratory infection.

The findings on physical examination were similar to those on the previous one. The findings on the electrocardiogram and the chest x-ray were normal. Repeated intravenous pyelograms showed progression of the pyeloureterectasia previously seen. After operation, described below, further dilatation of the ureters was demonstrable, especially on the left. At this time a cystogram showed the bladder to extend to the umbilicus, with reflux of dye entering both ureters.

Transfusions before and after operation maintained good hemoglobin levels, except for a fall to 7 gm. per 100 cc. preoperatively while the patient was given chloramphenicol therapy. At

From the Pediatric Service of the Bronx Hospital, Dr. J. H. Lapin, Attending Pediatrician.

1. (*a*) Swenson, O.; MacMahon, H. E.; Jaques, W. E., and Campbell, J. S.: A New Concept of the Etiology of Megaloureters, New England J. Med. **246**:41 (Jan. 10) 1952. (*b*) Swenson, O.: A New Concept of the Pathology of Megaloureters, Surgery **32**:367 (Aug.) 1952.

discharge the hemoglobin was 11 gm. per 100 cc. Frequent urinalyses showed specific gravities ranging between 1.004 and 1.020, albuminuria (trace to 2+), and many white and red cells, but no casts.

Urine cultures at frequent intervals revealed a changing flora, but mostly consisting of Bacillus pyocyaneus, B. proteus, and Streptococcus faecalis, in combination with or succeeding one another. The child was treated with repeated courses of penicillin, chlortetracycline (aureomycin), oxytetracycline (Terramycin), chloramphenicol, and polymyxin, depending on the sensitivity of the organisms at the time.

Other studies showed normal values for calcium, phosphorus, protein, albumin, globulin, blood sugar, and prothrombin. The blood urea nitrogen value reached 18 mg. per 100 cc. shortly after operation, but then returned to normal before discharge. Bleeding studies were done on admission and revealed normal bleeding and coagulation times and platelet counts.

At 15 months of age an operation disclosed atropic recti muscles superiorly and an enormously dilated thin bladder extending to above the umbilicus and reaching into the right flank. The bladder was opened, a contracture of the vesical neck was found, and a wedge resection of the bladder neck was done under direct vision. There was no urachus. Resection of part of the fundus and vault was performed and a suprapubic tube inserted, as well as a penile catheter.

The histological report by Dr. H. E. MacMahon[2] from the surgically excised tissues around the bladder neck reads as follows: "The mucosa is represented for the most part by a bare basement membrane. The submucosa is greatly thickened. Its vessels are distended and the areolar connective tissue is edematous, hemorrhagic, sclerosed and lightly infiltrated with inflammatory cells. The muscularis is both hypertrophied and hyperplastic. There are no ganglion cells. Since these sections are taken from the bladder neck, an area normally rich in ganglion cells, their absence would signify an aganglionic type of bladder."

The child was afebrile except for two days postoperatively and during two episodes of tonsillitis. He was fitted with a tight abdominal binder before discharge to a convalescent home. The suprapubic tube was left in place and the bladder irrigated daily. He was able to void through the penis and did so whenever the drainage tube became blocked.

Readmission to the hospital at 21 months of age after an attack of chicken pox revealed a hemoglobin value of 10.6 gm. per 100 cc. and a blood urea nitrogen value of 15 mg. per 100 cc. The urine showed 6 to 8 white blood cells and 4 to 6 red blood cells per high power field, a specific gravity of 1.012, and a 1+ reaction for albumin. Urine cultures grew a member of the Proteus group, sensitive to chloramphenicol, and subsequently one of the aerogenes group and a hemolytic Str. faecalis, sensitive to chloramphenicol, polymyxin, and erythromycin. Cystograms and intravenous pyelograms showed no significant changes from the findings of the previous examination. He was given separate courses with all three of the above antibiotics, as well as supplemental vitamins and iron. His subsequent gain in weight to 29 lb. (13,155 gm.) at 22 months of age and his early walking and talking were gratifying.

Case 2.—Baby K. (No. 252387), a boy, was born two months prematurely to a mother with persistent pyuria and albuminuria (trace to 1+) throughout pregnancy. He was delivered by low forceps; he was apneic at birth, breathed poorly after resuscitative efforts, and died one and one-half hours after birth. The weight was 2,000 gm. The child had multiple congenital anomalies, particularly absent abdominal musculature, with palpable abdominal masses, bilateral cryptorchidism, bilateral talipes equinovarus, umbilical hernia, and imperforate anus.

At autopsy it was noted in addition that the descending colon was distended and ended in a blind pouch in the area of the rectosigmoid, immediately posterior to the bladder at the inferior level of the latter. The right kidney was replaced by a very thin-walled cystic mass containing clear yellow fluid. The left kidney was replaced by multiple small cystic masses. The urinary bladder was markedly distended, and the bladder wall was very thin and showed no trabeculation. A complete obstruction was noted at the bladder neck. The right ureter was dilated to 1.0 cm., the left to 0.5 cm. The remainder of the postmortem examination showed nothing significant, except for bilateral atelectasis.

Histological section of the kidneys showed almost complete replacement by cyst tissue, with few glomeruli and occasional dilated tubules. The ureters, adrenals, liver, spleen, and lungs

2. MacMahon, H. E.: Personal communication to the authors.

showed congestion, and the latter showed atelectasis. Review of the bladder and ureter sections by Dr. MacMahon [2] showed only one ganglion cell in the bladder section and no ganglion cell at all in the section of ureter. This is consistent with a congenital defect of the sympathetic or parasympathetic nerve plexus.

CASE 3.—F. A. (No. 252119), a 3-month-old boy, was admitted to the Bronx Hospital from another city for study of multiple congenital anomalies. He was born with the right leg missing below the knee. This was the mother's second pregnancy and second delivery by Caesarean section, the first one having been for toxemia. The mother had had an operation for an abdominal tumor at a time when she was, unknowingly, about two weeks pregnant. The patient weighed 6 lb. 3½ oz. (2,820 gm.) at birth, but was born one month prematurely. At birth the absence of abdominal musculature had been noted. The child had developed normally. Physical examination revealed normal body measurements, absent anterior abdominal muscles, palpable liver and spleen, but not definitely palpable kidneys, bilateral cryptorchidism with the testicles in the inguinal canals, underdeveloped scrotum, and absent right leg 1 in. below the knee.

Laboratory findings were as follows: urinalysis, normal; serology, negative, and marked hypochromic microcytic anemia. X-rays of the chest and the extremities were normal except for the absent lower leg. Intramuscular pyelography was unsatisfactory.

The child was discharged on a regimen of iron and vitamins, to be returned for further studies. Due to illness he has been unable to return. His physician [3] provided us with the following report: Intramuscular pyelography showed the right kidney to be absent and a megaloureter on the left side in the upper third. Cystogram revealed an enlarged bladder and hypertrophy of the bladder mucosa; the ureteral orifices could not be visualized.

COMMENT

The syndrome of agenesis of the abdominal muscles with associated genitourinary anomalies is no longer considered a rarity. The three cases presented were seen in this hospital within three months' time. Several reviews have recently appeared.[4] Obrinsky [4e] reviewed 41 cases in 1949. In discussing the causes he mentions that obstructive uropathy has been adequately described and has not been found to be invariably associated with absent abdominal muscles; of the patients in his 41 cases only 2 showed obstruction. Two of our three patients showed definite organic vesical neck obstruction.

Daut, Emmett, and Kennedy [5] reported the case of a boy with this disease in whom a transurethral resection of the vesical neck was performed with improvement of urinary function. It is the belief of this group that obstructive uropathy is present, even though cystoscopy does not show it, even though the patient can

3. Effron, B.: Personal communication to the authors.

4. (*a*) Bruton, O. C.: Agenesis of Abdominal Musculature Associated with Genito-Urinary and Gastro-Intestinal Tract Anomalies, J. Urol. **66**:607 (Oct.) 1951. (*b*) Eagle, J. F., Jr., and Barrett, G. S.: Congenital Deficiency of Abdominal Musculature with Associated Genitourinary Abnormalities: A Syndrome; Report of 9 Cases, Pediatrics **6**:721 (Nov.) 1950. (*c*) Howard, P. J.: Congenital Absence of Abdominal Muscles and Genito-Urinary Malformation: Report of 2 Cases, Am. J. Dis. Child. **60**:669 (Sept.) 1940. (*d*) Mathieu, B. J.; Goldowsky, S.; Chaset, N., and Mathieu, P. L.: Congenital Deficiency of the Abdominal Muscles (with Associated Multiple Anomalies), J. Pediat. **42**:92 (Jan.) 1953. (*e*) Obrinsky, W.: Agenesis of Abdominal Muscles with Associated Malformation of the Genitourinary Tract: A Clinical Syndrome, Am. J. Dis. Child. **77**:362 (March) 1949. (*f*) Silverman, F. N., and Huang, N.: Congenital Absence of the Abdominal Muscles Associated with Malformation of the Genitourinary and Alimentary Tracts: Report of Cases and Review of Literature, ibid. **80**:91 (July) 1950.

5. Daut, R. V.; Emmett, J. L., and Kennedy, R. L. J.: Congenital Absence of Abdominal Muscles with Urologic Complications: Report on a Patient Successfully Treated, Proc. Staff Meet., Mayo Clin. **22**:8 (Jan. 8) 1947.

void with a good stream, and even though catheters can readily be passed. They feel that there is an imbalance between the detrusor urinae and the vesical neck and that a functional obstruction is present which can be relieved by vesical neck resection. In a recent article Greene and co-workers [6] presented five further cases in which the patients were thus treated with good results.

Of late several reports in the literature [7] have described the above syndrome associated with gastrointestinal anomalies, particularly malrotation of the colon. The disease is only rarely seen in girls.[8] Silverman and Huang [4f] described a girl who had only gastrointestinal and no genitourinary anomalies associated with the deficient musculature.

Megaloureter, not associated with abdominal muscle defect, has been reported for several years,[9] but Swenson and MacMahon [1] first related this defect to deficiency in the pelvic parasympathetic system and suggested a relationship to Hirschsprung's disease. In view of this recent work, sections of the bladder taken from the patients in Cases 1 and 2 were sent to Dr. Swenson and Dr. MacMahon for review. Their review of our sections showed deficiency of ganglion cells in areas which are normally provided with them. This finding is consistent with congenital megalobladder and megaloureter. In view of this finding another possibility of origin may be added to the ones already advanced in the literature,[10] namely, a congenital deficiency in the pelvic autonomic nervous system. This absence may explain the lack of improvement after operation in our Case 1. In connection with the detrusor-vesical-neck-imbalance theory it is conceivable that resection of the vesical neck may aid a bladder, deficient in but not devoid of ganglion cells, to empty itself more completely.[11]

In summary, the cases of three boys with the syndrome of absence of the anterior abdominal musculature associated with genitourinary and other anomalies have been presented. One patient has been operated on without significant change in his condition. An origin consisting of deficient pelvic autonomic nervous function has been suggested.

The operation in Case 1 was performed by Dr. M. L. Gottlieb and Dr. J. R. Herman. Dr. H. Skolnick, from the Pathology Department of the Bronx Hospital, performed the necropsy in Case 2. Dr. Swenson and Dr. MacMahon did the review of the sections in Cases 1 and 2, Dr. Effron provided the report on Case 3, Dr. J. R. Herman provided help and suggestions, and Dr. J. Felsen, Pathologist, and Dr. A. J. Bernstein, Roentgenologist, of the Bronx Hospital, gave assistance in this study.

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6. Greene, L. F.; Emmett, J. L.; Culp, O. S., and Kennedy, R. L. J.: Urologic Abnormalities Associated with Congenital Absence or Deficiency of Abdominal Musculature, J. Urol. **68**:217 (July) 1952.

7. Footnotes 1*a* and 4*f*.

8. Hofstein, J.: Absence congénitale des muscles abdominaux chez un nouveau-né du sexe féminin, Gynéc. et obst. **22**:23 (July) 1930. Footnote 4*d*.

9. Carver, J. H.: Megalo-Ureter: Report of 2 Cases, Brit. J. Surg. **36**:168 (Oct.) 1948. Heymann, W., and Martin, J. F.: Bilateral Megalo-Ureter in a Child: Return to Normal with Prolonged Control of Infection, J. Pediat. **35**:618 (Nov.) 1949.

10. Footnote 4*e* and *f*.

11. Footnotes 5 and 6.

Abstracts from Current Literature

Metabolism; Infant Feeding; Milk and Other Foods

Glucose Studies in Crocodilia. Ronald A. Coulson and Thomas Hernandez, Endocrinology **53**:311 (Sept.) 1953.

The picture presented here of glucose metabolism in the crocodile is qualitatively similar to that of the higher mammals but quantitatively very dissimilar.

It is not stated who held the five-foot subjects of this study.

Jacobsen, Buffalo.

Increased Survival of Liver-Fed Rats Administered Multiple Sublethal Doses of X-Irradiation. Benjamin H. Ershoff, J. Nutrition **47**:289 (June) 1952.

The average survival time of both immature and adult female rats following multiple sublethal doses of x-radiation was significantly greater on the liver-containing ration than on the other diets tested. The protective factor in liver was distinct from any of the known B vitamins. No significant difference in per cent or length of survival was observed following a single lethal dose of x-radiation.

Fredeen, Kansas City, Mo.

The Aspartic Acid, Glutamic Acid, Proline and Tyrosine Content of Meat. Alice M. Violante, Robert J. Sirny and C. A. Elvehjem, J. Nutrition **47**:307 (July) 1952.

The authors found that the average glutamic acid content of the skeletal muscle tissues was 16.5% of the crude protein; average aspartic acid content, 10.0%, tyrosine content, 3.5%, and proline content, 4.0%.

For the various organs, the average glutamic acid, aspartic acid, tyrosine, and proline contents were 14.9, 10.4, 3.7, and 5.0%, respectively.

Fredeen, Kansas City, Mo.

The Importance of Choline in the Prevention of Nutritional Edema in Rats Fed Low-Protein Diets. H. D. Alexander and R. W. Engel, J. Nutrition **47**:361 (July) 1952.

The data presented emphasize the greater importance of choline than protein as an edema-preventive agent. Whatever the mode of action choline may have in the prevention of edema resulting from malnutrition, it is quite clear that anemia and liver damage are abnormalities which appear earlier than the edema.

Fredeen, Kansas City, Mo.

A Brief History of Infant Feeding. William J. Davidson, J. Pediat. **43**:74 (July) 1953.

Davidson has written a brief but detailed account of the history of infant feeding. The paper should be read in its entirety.

Macdonald, Pittsburgh.

Caloric Intake in Relation to Physique in Children. Penelope S. Peckos, Science **117**:631 (June 5) 1953.

The subjects were children 6 to 14 years old, enrolled in a dental dispensary. A dietary diary was kept by each mother for a period of one week; from this the average daily intake of protein and calories was calculated. Each subject was classified under one of three categories; endomorphic, mesomorphic, and ectomorphic. A total of 86 subjects were studied, their caloric intake being compared with National Research Council standards.

It was found that the endomorphs (stocky) consumed on the average only 88% of National Research Council-recommended allowances, whereas the ectomorphs ate 103%. In the author's words, "This study indicates that the observed caloric intake of each of these groups relative to body build is actually in the opposite direction from the expected pattern."

It would appear, however, that in view of the small number of subjects studied, failure to break down data to account for sex differences in caloric intake, and the wide scatter of the observed values, the observations should be considerably extended before definite conclusions will be possible.

FORBES, Rochester, N. Y.

ESTABLISHING BREAST FEEDING. ALAN CHERRY, M. J. Australia **1**:844 (June 13) 1953.

The author pleads for a more natural regimé in the maternity hospital and better training of the practical nurses who care for the baby at home. With less emphasis on schedule and more attention to the normal demands of the infant and mother, more mothers will be able to nurse their infants.

McGUIGAN, Evanston, Ill.

THE PATHOGENESIS OF INFANTILE ATHREPSIA. E. KERPEL-FRONIUS, F. VARGA, and S. KOVACH, Ann. pædiat. **181**:129 (Sept.) 1953.

Hemodynamics, oxygen and water metabolism, and infections having a possible bearing on the origin of athrepsia were studied in 57 undernourished young infants. The characteristic syndrome of athrepsia seems to arise when previously wasted infants become chronically dehydrated. Anhydremia may appear in spite of high percentual water content of the body, because hemodynamically the absolute loss of blood plasma is of importance rather than relative values. Cardiac output may decrease to one-third of its normal value. Shock and anoxia, however, are milder than in toxicosis because of the already diminished O_2 requirements of the tissues due to malnutrition and semistarvation. The latter are severely augmented by decreased intestinal absorption due to chronic slowing of circulation; thus, starvation metabolism and acceleration of wasting, with only mild toxic symptoms, dominate the picture. In the last stages, an ever-progressing decrease in tissue oxidation sets in, leading to death from starvation. Chronic anhydremic slowing of circulation, accelerating the wasting of the body, is often due to infection by dyspepsia coli. Effective measures to prevent or treat the latter lead to a conspicuous decrease in the incidence of athrepsia.

FROM THE AUTHORS' SUMMARY.

THE HEPATIC FUNCTION IN INFANTS FED ON BREAST MILK AND ON AN ANIMAL MILK. P. PINNA and A. MARINI, Ann. ital. pediat. **6**:276 (June) 1953.

The frequency of some degree of hepatomegaly, and of dyspeptic, anaphylactic, and acetonic episodes in children fed on animal milk or animal milk and pap in their first year of life, has convinced the authors of the usefulness of comparative researches on the hepatic function of subjects fed respectively on human milk and on animal milk.

From the data resulting from the examination of glycemia, amino-acidemia, and cholesteremia; of the glycemic and amino-acidemic curves, and of postadrenal and postinsulin glycemic curves, the authors are sure that the children fed on animal milk frequently show, even after some time, signs of altered hepatic function, chiefly with regard to glycoregulation.

The authors think that the main cause of such hepatic insufficiency must be sought in a more intense work of deamination which the organ must do for cow, sheep, or goat milk because of the different and greater protein contents, but they do not exclude the eventual responsibility of the different percentages of fatty acids.

FROM THE AUTHORS' SUMMARY.

OBESITY IN CHILDREN, AS ENCOUNTERED IN ONE'S PRACTICE. G. SALVIOLI, Clin. pediat. **35**:207 (April) 1953.

Data as to the incidence and causes of obesity in children has been gathered from examinations of about 8,000 children seen in the out-patient clinic and 2,000 on home visits in Bologna. In the war years, the incidence of obesity was 0.96%, while 10 years later, in 1951-1952, it was 3.82%. The greatest incidence of obesity was in the 3-year-old children; the 8-year-old and the 11-year-old children were also more prone to obesity. Overeating is doubtless the major cause of obesity; this may be due to eating habits, and occasionally be secondary to an organic disturbance of the hypothalamus or to infection. The child may become overweight due to a tendency to hypoglycemia, or due to storage of water in the tissues. Salvioli concludes that the main causes of obesity in children are overeating and a diathesis secondary to an infection.

HIGGINS, Boston.

STUDIES IN CHILDREN AFFECTED WITH MALNUTRITION: XI. ENZYMATIC ACTIVITY OF DUODENAL CONTENTS IN CHILDREN AFFECTED WITH THIRD-DEGREE MALNUTRITION. FEDERICO GOMEZ, RAFAEL RAMOS GALVAN, JOAQUIN CRAVIOTO, SILVESTRE FRENK, and JUDITH VAZQUEZ. Bol. med. hos. infantil **10**:106 (April) 1953.

The authors report on the enzymatic activity of duodenal contents in 40 children complaining of third-degree malnutrition; such activity was found diminished, especially the figures for lipase.

A notable increase in the enzymatic activity was seen in our patients when their nutritional condition improved, but no correlation was found between the figures for serum albumin and the amount of pancreatic enzymes. Also, no correlation was seen between enzymatic activity and appetite. Nonmodified proteins (gelatin) were absorbed more slowly than those that underwent a modification previous to their ingestion (Casec).

The finding of diminished enzymatic activity both in kwashiorkor and in third-degree malnutrition is another fact that helps to categorize both diseases as syndromes which, in the majority of cases, have as a common cause a chronically low food intake.

FROM THE AUTHORS' SUMMARY.

ANEMIA IN MALNUTRITION. JOAQUIN M. CRAVIOTO, SILVESTRE FRENK, FEDERICO GOMEZ, JUDITH VANQUEZ SANTSELLA, and RAFAEL RAMOS GALVAN, bol. med. hosp. infantil **10**:236 (June) 1953.

The authors report a study of 51 children affected with malnutrition, in whom determinations were made of red blood cells and blood volume, with the idea of finding out the frequency and type of anemia they showed. The figures for hemoglobin and erythrocytes considered according to the usual techniques show there is a moderate anemia associated with malnutrition.

From the morphological point of view, the type of anemia most frequently found is normocytic and normochromic. Owing to the increase of plasma volume in these children, the anemia must be considered as of the hypervolemic type. In those cases of severe anemia, where found, there were superadded pathologic processes, other than malnutrition, which increased the intensity of the anemia.

FROM THE AUTHORS' SUMMARY.

A NEW METHOD TO PRESERVE RAW HUMAN MILK. W. CATEL, J. PENDL, and O. SCHIFF, Deutsche med. Wchnschr. **78**:1137 (Aug. 28) 1953.

The authors discuss a new method of preserving raw human milk. The method consists of lyophilizing frozen human milk. The resulting powder is readily water-soluble. Antibacterial substances ferments and vitamins are not destroyed. Only vitamin A activity is reduced.

AMBERG, Rochester, Minn.

NOURISHMENT PROTEIN AND NITROGEN RETENTION. OTTO TEZNER, Acta pædiat. **181**:177 (Sept.) 1953.

Ten infants aged between 23 days and 5½ months were fed on half-milk for one week and subsequently for another week on concentrated buttermilk. The increased protein in the food led to an increase of the retained nitrogen in nine cases, which rose in two cases to 44 and 45% respectively. The infant in whom the rise was 44% developed toxicosis.

It is surmised that an overdose of protein may lead to toxic disturbances, and in connection with this idea the concept of toxicoses is discussed.

FROM THE AUTHOR'S SUMMARY.

KWASHIORKOR. E. JANSSEN, Maandschr. kindergeneesk. **21**:281 (Sept.) 1953.

Kwashiorkor is a disease of childhood which affects especially the older baby and the young child. It is caused by a prolonged faulty diet which greatly lowers the child's resistance to infectious diseases. These infectious diseases may influence the clinical picture to an important degree, but they are not the primary cause.

Kwashiorkor develops into a syndrome if the nuclear symptom, i. e., arrest of growth, is not treated in good time. The syndrome finally gives rise to a clinical picture which depends upon the combination of dietary errors; for instance, in a country where pellagra develops easily,

kwashiorkor has a pellagroid aspect, but is not true pellagra. Treatment should be directed against the central symptom; the most efficient therapy is by acid milk preparations. Symptomatic treatment should be added as soon as possible. The return to a normal diet should be gradual.

The physician should have a good training in pediatrics; a long experience of pediatric nursing is indispensable for the nursing staff. Prevention on a large scale is possible only with the help of the numerous small and larger missionary posts, as they know the language and the tribal customs. Government institutions are not equipped to effect anything in this field, particularly as regards prevention in the interior. The education of primitive man to a social being requires means other than purely medical advice.

FROM THE AUTHOR'S SUMMARY.

Vitamins; Avitaminoses

THE EFFECT OF VITAMIN T (GOETSCH) ON CHILDREN WITH DEVELOPMENTAL RETARDATION AND UNDERWEIGHT. W. Muelhauser, Monatsschr. Kinderh. **101**:13 (Jan.) 1953.

Thirty-four underweight children institutionalized because of mental and developmental retardation received oral vitamin T (Goetsch) for five months. They were observed for one and one-half years. Ages ranged from 4 to 16 years. Sixty-six per cent of the patients treated showed greater weight gains than during the entire year prior to therapy. In the age group of from 10 to 16 years weight gain was 240%, in the 4-to-10-year group 160%, above expected weight increments.

HARTENSTEIN, Syracuse, N. Y.

Hygiene; Growth and Nutrition; Public Health

ADOLESCENTS IN TROUBLE. L. B. BLESSING, Bull. Tulane M. Fac. **12**:99 (May) 1953.

The author points out that just to be an adolescent is to be in trouble. Adolescents not having sympathetic understanding from family and community are often in trouble, and then can only be helped by proper juvenile court, probation department, and treatment facilities. The adolescent is entitled to understanding parents, a tolerant, protective, and understanding court, correction instead of punishment, a good probation department, and an enlightened and cooperative community.

McGUIGAN, Evanston, Ill.

INFANT DEATHS IN THE SINGUR HEALTH CENTER CENTRAL AREA (WEST BENGAL), 1947-1952. MUKTHA SEN, Indian J. Pediat. **20**:67 (March) 1953.

A survey of infant deaths in the Singur Health Central Area from 1947 to 1952 showed a decline in the mortality rate from 163.4 to 105.57 during that period. Causes of death are divided into neonatal deaths and deaths under 1 year. The most frequent cause of death in the neonatal groups was prematurity, which accounted for 41.12% of the mortality. By contrast, the second groups showed diarrhea, causing 25%; respiratory infections, 16%, and malnutrition, 9% of the deaths.

McGUIGAN, Evanston, Ill.

AN INVESTIGATION INTO THE INFANT MORTALITY RATE. S. B. SACHS, South African M. J. **27**:681 (Aug. 15) 1953.

The author has devised a method of computing infant mortality rates, which he urges should be used in order to give more accurate figures.

McGUIGAN, Evanston, Ill.

CONSIDERATIONS ON THE CAUSES OF THE ELEVATION OF THE INFANT MORTALITY RATE IN 1949 AND PROPOSED REMEDIES. JUAN L. MORALES Y GONZÁLEZ, Acta pediat. espaň. **10**:916 (Nov.) 1952.

The rate of infant mortality rose in 1949 in all of Spain but especially in Seville. The author points out that some factors are real and some apparent.

The failure of harvests due to weather conditions and the discontinuation of the Maternal and Child Health Act are very real ones. This had been in effect since 1941, and for comparison the author shows the fall in infant mortality in the years from 1942-1948. Two hundred seventy

child health centers were closed, 10 of them in Seville, where the population is mostly rural.

There was a very inadequate staff of doctors and visiting nurses during 1949. In 101 villages in Seville there were only 6 where the health centers were maintained.

Among the factors which is more apparent than real was the lowered birth rate during this year also.

Many graphs and tables are included. ALLEN, San Francisco.

MEDICO-SOCIAL ASPECTS OF ADOPTION AND BOARDING HOMES AS FORMS OF PROTECTION FOR ABANDONED CHILDREN. M. ZAMORA TIFFON, Arch. pediat. **3**:283 (Nov.-Dec.) 1952.

The author gives the history of the handling of dependent and abandoned children. He compares some of the laws in various countries. The necessity of placing of babies in a healthy family is of interest to the physician because of the many disturbances formerly thought to be hereditary but now known to be due to faulty environment in early infancy. This is true in many areas from nutrition to psychosexual development. ALLEN, San Francisco.

NEW METHOD OF GRAPHIC REPRESENTATION OF GROWTH. M. SUAREZ and J. TEIJEIRA, Rev. españ. pediat. **8**:439 (July-Aug.) 1952.

The authors present a new method of graphic representation of growth which permits the visualization of any factor with chronological age. The developmental age, velocity, and direction of growth may be plotted without reference to tables. They believe it to be simpler and more mathematically correct than the Wetzel grid. ALLEN, San Francisco.

CRITICAL STUDY ON SOMATIC GROWTH: II. MANUEL SUÁREZ, Rev. españ. pediat. **8**:571 (Sept.-Oct.) 1952.

This is a critical study of the methods which have been elaborated over a period of years, beginning with Quetelet in 1871. The use and misuse of such data are discussed. The indices used by some of the best known of the investigators are included, with samples of the various graphs, curves, and grids.

All of them are incomplete in method and must be used with other measurements in a complete study of the actual maturity of a given child. ALLEN, San Francisco.

CRITICAL STUDY OF GRAPHIC METHODS OF SHOWING GROWTH AND DEVELOPMENT: III. MANUEL SUÁREZ, Rev. españ. pediat. **8**:595 (Sept.-Oct.) 1952.

This is a continuation of the study of methods of showing growth and development. In this study, however, the author goes into greater detail on certain methods which he considers the best. The methods explained are those of Bayer and Gray, Karlberg and Permans, Sontag and Reynolds, Alson and Hughes, and Wilkins.

The grids of de Toni, with the modifications of Gobesi and Tatafiore, seem to be the first to use the term auxograph. The result on these grids is an equilateral triangle in normal children.

The somatogram of Schleissner and the three dimensional diagram of Odegard become more mathematical, and the Wetzel grid is the climax of these mathematical exercises. The author feels it has all the inconveniences of the older methods and calls renewed attention to the old axiom "Every child is his own standard of comparison."

The methods of Correnti and Tanner are revived, and attention is called to that of Suárez and Teijeira previously reviewed. ALLEN, San Francisco.

INDICES OF MUSCULAR DEVELOPMENT: GROWTH AND DEVELOPMENT. IV. M. SUÁREZ and J. PENA, Rev. españ. pediat. **8**:633 (Sept.-Oct.) 1952.

This is the fourth in a series of studies on growth and development and deals with the relation of muscular mass to the excretion of creatinine.

The study shows that the quantity of creatinine excreted in 24 hours rises progressively with the age and the weight. The amount of the increase is proportional to the increment in the muscle mass. ALLEN, San Francisco.

INDICES OF MUSCULAR DEVELOPMENT: GROWTH AND DEVELOPMENT: V. M. SUÁREZ and J. PENA, Rev. españ. pediat. **8**:653 (Sept.-Oct.) 1952.

This study gives the technical details of a study made of the muscle mass in the thighs of 192 children. The area of radiographic projection was determined. The technique devised by Stuart and the planimeter by Coradi were used. The relation of this area of projection plotted with the age, weight, and height is shown, and its use as an index of muscular development is discussed.

ALLEN, San Francisco.

INDICES OF MUSCULAR DEVELOPMENT: CORRELATION BETWEEN CREATININURIA AND RADIOGRAPHIC MUSCULAR AREA; GROWTH AND DEVELOPMENT; VI. M. SUÁREZ and J. PENA, Rev. españ. pediat. **8**:663 (Sept.-Oct.) 1952.

In this study of growth and development, the two previous studies regarding creatinine excretion and muscular development are evaluated as indices of development. Many cuts of the x-rays are included. Both methods are good indices of muscular development.

The nutritional state and certain pathological conditions may be discovered by radiographic method.

ALLEN, San Francisco.

INFANT MORTALITY IN CHILE ACCORDING TO GEOGRAPHIC ZONES. JOSE M. UGARTE, Rev. chilena pediat. **22**:365 (Sept.) 1951.

The author studied the evolution of the chilean infantile mortality by geographical zones. Infantile mortality in Chile has dropped considerably from 247 per thousand in 1920 to 196.6 in 1940 and finally to 140 in 1950. This drop is not uniform throughout the country, with a mean average descent of 32.5% for the whole country, some provinces having attained a 55.3% and others only a 9.9% decrease in the 27 years that this study covers. An analysis is made of the possible causes that might have influenced these figures.

FROM THE AUTHOR'S SUMMARY.

LEGAL AND SOCIAL PROTECTION OF BREAST FEEDING IN URUGUAY. CARLOS A. BAUZA, Arch. pediat. Uruguay **23**:539 (Aug.) 1952.

The author reviews the national legislation aimed at protecting breast feeding function. Some antecedents are revealed. Actual legislation is analyzed and commented through the following framework: concession of time for breast feeding, possibility of mother-child association, conservation of the economic welfare of the home, protection of the right of the wet nurse's son to his mother's breast milk. The role of cultural factors and emotional attitudes are stressed.

FROM THE AUTHOR'S SUMMARY.

ACCELERATION AND AGE DISPOSITION. BERNFRIED LIEBER, Arch. Kinderh. **144**:11 1952.

Our concepts and statistical statements concerning age disposition need correction. This becomes evident from a thorough study of children admitted over a period of 30 years at the University Children's Hospital in Jena. The manifestations of rheumatic disease occurred in a younger age group during the last decade.

It could be demonstrated by the analysis of 776 first attacks of rheumatic syndrome that the cardiac involvement before the age of 9 years was more frequent from 1941 to 1949 than from 1917 to 1928. Conversely, poliomyelitis has affected the adolescent and adult age group in a higher percentage during recent years.

Adult forms of tuberculosis are more frequently under the care of the pediatrician. The earlier onset of puberty might be one etiological factor in the interesting phenomenon of age shift, but unknown causes must play an important part.

GOTTSTEIN, Chicago.

ON THE PLANNING OF UPBRINGING IN CRÈCHES. J. KOCH, Pediat. listy **8**:97 (June) 1953.

The author describes the difficulties and deficiencies in the upbringing of children in crèches and indicates how to overcome them. A proposed case book for the planning of upbringing is appended.

FROM THE AUTHOR'S SUMMARY.

Results of Microbiological Check-Ups in Crèches. K. Znamenacek, J. Syrucek, and J. Jelinkova, Pediat. listy **8**:101 (June) 1953.

For a period of six months the authors followed the microbiological state of the mucous membrane of the upper respiratory passages in crèche children and workers and also the atmospheric and dust conditions of the crèche environment. By comparison with a group of non-crèche children it was found that between the two groups of children there are no qualitative differences in the bacterial flora. The quantitative differences were not sufficiently great to account for the greater sickness rate among crèche children. Also the serological groups and types of the beta hemolytic Streptococcus showed the usual prevalence of the various types, with no proved relationship to the sickness rate. The findings of microbes in the environment can be taken only as an index of hygiene in the crèche. Bacteriological examination for its own sake is of no practical value if it is not linked with the following of the clinical condition and epidemiological situation in the surroundings of the children. The basic influence upon the sickness rate of children in crèches should be sought in the reactibility of the child's organism. Of microbiological influences the virus component is of main importance.

From the Author's Summary.

Prematurity and Congenital Deformities

Calcium and Phosphorus Studies in Negro Premature Infants. Morris Gleich, Saul Smoller, and Beatrice E. Scott, J. Pediat. **39**:677 (Dec.) 1951.

Premature infants are very susceptible to rickets. Negro infants are prone to develop rickets. These Negro premature infants were fed half-skim milk or evaporated milk formulae supplemented with 1,000 U. S. P. units of vitamin D daily. Biochemical and x-ray studies were conducted. One of the authors thought that these infants might have subclinical evidence of rickets at the time of discharge from Harlem Hospital, but they did not.

Macdonald, Pittsburgh.

Feeding the Premature. S. Gorham Babson, Northwest Med. **51**:596 (July) 1952.

The author presents a guide offering safe limits for feeding premature infants, which is recommended where premature service is small or experience limited. Eight practical considerations pertinent to the care and feeding of small premature infants are listed, and a guide is presented in graph form with rather exact daily quantitative and qualitative increases in formula strengths for premature infants of various weights. The limitations of the feeding guide are outlined in the practical considerations listed.

Docter, Seattle.

Bicephalic Monster: A Case Report. Jackson E. Livesay, Ernest P. Griffin, and Daŝ H. Sheeran, Radiology **58**:239 (Feb.) 1952.

A roentgenogram of the pregnant abdomen showed two fetal spines coming together at a single pelvis and only one set of lower extremities. These findings accounted for a correct prenatal diagnosis. Roentgenograms after delivery showed two heads, four arms, fusion of the thoracic cages, two spines, one pelvis, and only two legs. Fifteen previous cases have been reported in the literature.

Anspach, Chicago.

Excessive Intake of Vitamin A as a Cause of Congenital Anomalies in the Rat. Sidney Q. Cohlan, Science **117**:535 (May 15) 1953.

Administration of 35,000 I. U. of vitamin A daily to pregnant rats from the 2nd to the 16th day of gestation resulted in the production of congenital anomalies in the litters and a reduction in the number of litters carried to term.

A control group of 50 rats produced 44 litters with a total of 410 apparently normal newborn, whereas 100 rats given excess vitamin A produced and carried to term only 10 litters with 72 offsprings, and 54% of these exhibited gross anomalies. The authors did not study the effects of smaller doses of vitamin A. It is to be noted that the dosage of vitamin A employed in these studies was of the order of 180,000 units per kilogram per day.

Forbes, Rochester, N. Y.

THE TREATMENT OF CLEFT LIP AND PALATE IN SOUTH AFRICA. JACK PENN, G. CLAYDEN, and H. BENTEL, South African M. J. **27**:484 (June 6) 1953.

Five hundred cases of cleft lip and palate repair are analyzed. The authors conclude that such repair is not within the scope of the general surgeon. Careful anesthesia is an essential, as is follow-up, with the help of the orthodontist, prosthetist, and speech therapist. Half of the present series had been incorrectly operated on, with resulting physical and psychological suffering and financial and psychological strain on the parents. Attention is called to various services available in this country and supported by the state, which the authors feel is the proper way in which to handle such cases. They feel that only fully trained personnel should be permitted to handle these cases.

McGUIGAN, Evanston, Ill.

RARE COMBINED MALFORMATIONS. P. BORGER, Ann. pædiat. **181**:161 (Sept.) 1953.

In the introduction, the problem of malformations, especially combined malformations, is reviewed and the question of the pathogenesis is explained by quoting well-known examples. Then two cases of Bonnevie-Ullrich status, one an "atypical chondrodystrophy" and the other the so-called "Turner syndrome" (Bonnevie-Ullrich status in the narrower sense), are described in detail. The importance of glandular disturbances, in this case hyperthyroidism, as genetic factors especially for these two combined malformations is discussed, and finally, after mention of therapeutic possibilities, the difficulties of the differential diagnosis against clinical pictures of similar malformations are pointed out.

FROM THE AUTHOR'S SUMMARY.

CONGENITAL DEFICIENCY OF ABDOMINAL MUSCULATURE WITH ASSOCIATED GENITOURINARY ABNORMALITIES. KURT KAIJSER, Ann. pædiat. **181**:173 (Sept.) 1953.

A case of laxity of the abdominal muscles due to congenital agenesis, hydronephrosis, and cryptorchism in a boy is presented. His condition has been observed from his birth until the age of 4½ years. Despite the marked malformation of the urinary tract, his general condition has been good, and no infection of the urinary tract has manifested itself.

FROM THE AUTHOR'S SUMMARY.

PFAUNDLER-HURLER'S DISEASE (GARGOYLISM). U. GUELI and F. SEVERI, Pediatria **61**:434 (May) 1953.

A boy 23 months of age, an only child, presented typical findings of gargoylism, including physical and mental underdevelopment, the facies, corneal opacity, macroglossia, hypertrichosis, enlarged tonsils, hydrocephalus, hepatomegaly, and a hypercholesterlemia. Reilly's granulations were observed in 8% of the white blood cells.

HIGGINS, Boston.

MACRODACTYLISM WITH SYNDACTYLISM. J. GARRIDO LESTACHE, Acta pediat. españ. **10**:987 (Dec.) 1952.

The case of a 5-year-old girl with syndactyly of the second and third toes of the left foot from birth is presented. The macrodactylism developed later and rapidly until the child was unable to wear hose or shoes.

The longitudinal axis on the left foot was 21.3 cm., while on the normal foot the mass grew vertically also. X-ray showed bones, as well as soft tissue, participating in the excessive growth. Treatment was surgical and was important not only for the child's comfort but also because there are cases of malignant tumors which have been reported when surgery was not used. There are photographs and x-rays, and the surgical procedure is described.

ALLEN, San Francisco.

VITAMIN T AND PREMATURITY. TORRES MARTE and FERRER PI, Arch. pediat. **3**:293 (Nov.-Dec.) 1952.

The authors present results of a study of nine premature babies studied from birth to 3 months of age. No form of vitamin other than vitamin T was added to breast milk, nor were amino acids given. Graphs illustrating weight, length, and cephalic measurements showed very satisfactory results.

The time needed for recovery of birth weight was appreciably shortened. The authors feel vitamin T has an important place in care of premature babies but admit the number studied is small as a basis for any definite conclusions other than that the infants so treated did better than untreated infants or those given amino acids.

ALLEN, San Francisco.

PROTEIN SUPPLEMENTS IN THE FEEDING OF PREMATURE INFANTS. KLAUS SEELEMANN and KLAUS WATERSTRADT, Monatsschr. Kinderhe. **101**:219 (April) 1953.

Thirty premature infants were fed boiled human milk with added calcium caseinate; 30, a mixture of amino acids (produced by acid hydrolysis with the addition of the missing essential amino acids) added to the above described milk, and 30, the milk without protein supplement added. All infants received 100 mg. of ascorbic acid added to the milk.

No significant differences between the two groups receiving protein supplements were noted in regard to weight gain, hemoglobin, infections, digestive disturbances, and serum proteins.

HARTENSTEIN, Syracuse, N. Y.

ELECTROENCEPHALOGRAM OF PREMATURES. H. MAI, E. SCHUTZ, and H. W. MILLER, Ztschr. Kinderh. **69**:251, 1951.

Damages to some silent areas of the brain, particularly in premature infants, may not be noted until several years later. The diagnosis of such damages presumes, however, the knowledge of the normal electroencephalogram of the premature infant.

The electroencephalogram of premature infants under special precautions shows similar findings to the tracings of newborn infants which, however, appear somewhat later and less pronounced. The presence of longer lasting rhythmical waves in sleeping premature infants resemble those of subcortical rhythms of animal experiments. Slow arhythmical waves dominate the tracings of prematures similar to those of the newborns. The first α waves appear in the newborn infant around the fourth month of life over the central region and similarly also in premature infants around the same time but in a less marked form.

GLASER, Jerusalem.

CONGENITAL ANOMALIES OF THE UPPER LIMB. Z. NEJEDLA, Pediat. listy. **7**:171, 1952.

A description of 10 congenital abnormalities of the upper limb is given. These occurred between January, 1948, and January, 1950, in 5,359 deliveries (0.18%) at the Institute for the Care of Mother and Child, in Prague.

FROM THE AUTHOR'S SUMMARY.

THE DEATH OF PREMATURE INFANTS DURING THE FIRST YEAR OF LIFE. K. POLACEK, Pediat. listy. **7**:201, 1952.

A group of 405 premature infants and 3,000 mature infants were followed during the course of the first year, and the deaths and causes of death were studied in the two groups. The most interesting observation was that the influence of prematurity on the death rate is apparent in slightly premature infants for the first 3 months of life and in the more immature infants to the end of the first 6 months. In the second half of the first year the difference between the two groups disappears.

FROM THE AUTHOR'S SUMMARY.

PECTORAL MUSCLE DEFECTS. MATHILDE L. M. HOUBEN, Maandsschr. **21**:308 (Sept.) 1953.

After a review of the Dutch literature on pectoral muscle defects and other concomitant anomalies, four personal observations of unilateral chest deformities are described. One patient had a dextroposition of the heart. The causative factors of these anomalies are discussed. Surgical intervention is not indicated in most cases.

FROM THE AUTHOR'S SUMMARY.

STUDIES ON CARBONIC ANHYDRASE ACTIVITY IN CHILDREN. RAGNAR BERFENSTAM, Acta pædiat. **41**:297 (July) 1952.

An account of the results of intravenous and intramuscular injections of whole blood, plasma, and serum into premature infants is given. In all cases there is an increase of carbonic anhydrase activity in the infant's blood.

The cause for the increase in enzyme activity is discussed. This is found to be probably due to an activating factor in plasma; this factor is thermostable, dialystable, and seemingly of non-electrolyte character.

The possible inconveniences that premature infants could suffer on account of their low carbonic anhydrase activity and the help possibly afforded to these infants by transfusions are discussed.

FROM THE AUTHOR'S SUMMARY.

CARBONIC ANHYDRASE ACTIVITY IN FETAL ORGANS. RAGNAR BERFENSTAM, Acta pædiat. **41**:310 (July) 1952.

The author has investigated the carbonic anhydrase activity in organs from fetuses and premature infants and has shown that the activity in certain organs, such as kidney and stomach, surpasses that in the blood of fetuses of corresponding age. The significance of the enzyme activity in the fetal organs is discussed.

FROM THE AUTHOR'S SUMMARY.

THE CLAW HAND IN GARGOYLISM, ITS PATHOLOGY AND TREATMENT. STIG SJULIN and TORD SKOOG, Acta pædiat. **41**:563 (Nov.) 1952.

Gargoylism is discussed briefly as a systemic disorder, and a typical case is reported in detail. Claw hand, a characteristic symptom, is shown to be due to a trigger-finger condition and was completely cured surgically in this case. The origin of trigger finger in gargoylism is discussed, and the advantage of overcoming the hand deformity is stressed. Further, a surgical reduction of the tongue was carried out in this case to relieve the breathing difficulties caused by macroglossia.

FROM THE AUTHORS' SUMMARY.

RETROLENTAL FIBROPLASIA: ANIMAL EXPERIMENTS. LARS J. GYLLENSTEN and B. O. E. HELLSTROM, Acta Pædiat. **41**:577 (Nov.) 1952.

The following changes have been found in the eyes of 1 to 3-week-old full-term mice that were exposed to pure oxygen intermittently from birth: hemorrhages; retinal folding, and formation of a vascular, cellular, and fibrous tissue in the vitreous body.

FROM THE AUTHORS' SUMMARY.

ACROCEPHALOSYNDACTYLY. J. A. BOOK and L. HESSELVIK, Acta pædiat. **42**:359 (July) 1953.

A case of acrocephalosyndactyly is described. The parents and sibs have been examined by the writers. A pedigree is given and the clinical and genetic features of this rare malformation briefly reviewed.

FROM THE AUTHOR'S SUMMARY.

CONGENITAL ABSENCE OF THE ABDOMINAL MUSCLES ASSOCIATTED WITH GENITAL URINARY MALFORMATION. J. BJERRUM, Nord. med. **46**:1274 (Aug.) 1951.

The author reports a typical case of the well-known combination of malformations, namely, congenital absence of the abdominal muscles, hypertrophy and dilatation of the urinary bladder, dilatation of the ureters and the renal pelvis, and a bilateral cryptorchidism. Some of the children are suitable for surgical treatment, which must be made as early as possible. The purpose of this treatment must be to facilitate an easier outflow from the bladder.

WALLGREN, Stockholm, Sweden.

DIAGNOSIS OF ANENCEPHALUS BEFORE PARTURITION. EVERT GUSTAVSSON, Nord. med. **46**:1874 (Dec.) 1951.

Twenty-five cases of anencephalus occurred at the Department of Gynecology, Norrköping, Sweden, between 1931 and 1950. Thirteen were diagnosed prior to delivery, mainly by routine roentgenologic examination of all cases with hydramnios.

WALLGREN, Stockholm, Sweden.

Newborn

TRACHEAL DIAMETER IN THE NORMAL NEWBORN INFANT. ARTHUR C. TOMPSETT JR., Am. J. Roentgenol. **67**:785 (May) 1952.

Observation of the tracheal diameter of 350 infants 24 hours after birth revealed that the average antero-posterior diameter of the newborn tracheal lumen is 4.5 mm. at the fifth cervical segment, 3.9 mm. at the first thoracic segment, and 3.5 mm. at the third thoracic segment.

HODGSON, Rochester, Minn.

EFFECTS OF VARIOUS TYPES OF ANALGESIA AND ANESTHESIA ON THE NEWBORN. CLAIR M. CAREY, Illinois M. J. **102**:256 (Oct.) 1952.

A survey of the delivery records from June, 1950, through December, 1950, of the West Suburban Hospital, Oak Park, Ill., was made to ascertain the relationship of asphyxia neonatorum to premedication, anesthesic, and length of labor. Of 1,784 deliveries, only 10.20% of the infants showed some degree of asphyxia. All infants showing moderate to severe asphyxia required some degree of resuscitation and are included in this study.

Anesthetic agents were used only at the time of delivery, whether spontaneous or operative, and during the time of necessary repair, if any. Of the infants requiring some degree of resuscitation, nitrous oxide was used in 3.85%; ethylene in 7.96%; ether in 33.3%; nitrous oxide and ethylene in 8.31%; ethylene and ether in 30%; nitrous oxide, ethylene, and ether in 44.44%; no anesthetic in 2.88%.

Of the asphyxia cases the following types of premedications were administered to the mother: meperidine (Demerol) hydrochloride 8.02%; meperidine hydrochloride and scopolamine hydrobromide 8.30%; barbiturates 16.66%; morphine sulphate, meperidine hydrochloride, and scopolamine hydrobromide 16.66%; no premedication 20.54%. A factor influencing the relatively high incidence of asphyxia in the group with no premedication was the type of labor. It includes operative cases, including those in which the birth canal was inadequate for vaginal delivery.

In the relation of the length of labor to the incidence of asphyxia neonatorum, labors under 12 hours' duration resulted in only 9.27% of the asphyxia cases. There is a marked increase in asphyxia as the labor extends beyond the 24-hour period. In this group approximately one out of every four required some degree of resuscitation.

Following a review of the literature, Carey concludes by placing an emphasis on the need for individualizing each obstetrical case before the administration of either analgesia or anesthesia.

BARBOUR, Peoria, Ill.

ANOXIA IN THE NEWBORN INFANT. E. T. MCENERY, Illinois M. J. **102**:374 (Dec.) 1952.

Anoxia is a serious complication for the newborn infant. Prophylactically good obstetric management is needed during the entire pregnancy. For the care of the infant at birth, clear the airways; administer oxygen; provide heat; withhold fluids for a few days to lessen edema of the brain. Constant observation is necessary, since changes take place very rapidly.

BARBOUR, Peoria, Ill.

NEONATAL MORTALITY. J. JHIRAD, Indian J. Child. Health **1**:536 (Nov.) 1952.

Factors in the production of high neonatal mortality are reviewed. The usual conclusions are drawn: Prevention of prematurity, good pre- and intranatal care, carefully planned delivery, and adequate pediatric care in the nursery are essential means for reducing mortality.

MCGUIGAN, Evanston, Ill.

ACUTE PULMONARY EDEMA IN THE NEWBORN. C. UNGARI and E. JASIELLO, Arch. ital. pediat. e puericolt. **15**:236, 1952.

The authors record a case of a newborn child dying after 34 hours of life and showing the clinical symptomatology and the anatomohistologic picture of cerebral and pulmonary edema.

They describe another case, which recovered, whose clinical picture suggested similar morbid modifications. Having discussed the different etiopathogenic mechanisms of acute pulmonary edema, they suggest that in the two cases the acute pulmonary edema took place through a neurogenic mechanism and on the basis of a cerebral edema, which, in its turn, is connected with parturition trauma.

FROM THE AUTHORS' SUMMARY.

THE IMPORTANCE OF A RADIOLOGICAL STUDY OF INTRACRANIAL HEMORRHAGE OF THE NEWBORN AND ITS SEQUELAE. C. TORRICELLI, Clin. pediat. **34**:73 (Feb.) 1952.

Data from a radiological study of 20 patients who had an intracranial hemorrhage are presented. Pneumoencephalography and angiography, as well as direct radiology, were used. Among the sequelae pictured were hydrocephalus, microcephaly, and porencephaly.

HIGGINS, Boston.

TWO CASES OF MENINGOCOCCIC MENINGITIS IN THE FIRST WEEK OF LIFE. E. MARTINEZ CARMONA and J. VINCTA TEIZIDO, Rev. españ pediat. **7**:835 (Nov.-Dec.) 1951.

The authors present case histories of two infants who developed meningococcic meningitis on the second and fourth day of life, respectively. Diagnosis was made clinically by spinal puncture smears and culture of spinal fluid. The two infants were treated with penicillin intrathecally once, followed by penicillin intramuscularly.

Abnormal spinal fluid findings and symptoms disappeared completely by the 24th day of life. One child was seen in a follow-up study on the 40th day of life and showed no sequelae.

ALLEN, San Francisco.

EPIDEMIC DIARRHEA IN THE NEWBORN. J. DVORAK, B. KOTT and VACLAVEK, Pediat. listy **6**:213 (July) 1951.

The etiology, clinical features, prophylaxis, and treatment are described. A short statistical note on the epidemics in the hospitals of Most and Chomutov is given.

FROM THE AUTHORS' SUMMARY.

THE CLINICAL ASSESSMENT OF FETAL ERYTHROBLASTOSIS. K. POLACEK, Pediat. listy **7**:147 (May-June) 1952.

The investigatory steps taken in our institution in establishing a diagnosis of fetal erythroblastosis are described with the aim of establishing the precise indications for exchange transfusion. The aim of antenatal examinations (history, serological examinations) is to foresee the possibility of fetal erythroblastosis. An exact assessment must be made after birth, and this depends in the first place on the determination of the hemoglobin and bilirubin in the umbilical blood (also clinical and serological examination). Exsanguination transfusion is indicated when the hemoglobin falls below 11.5 gm. or the bilirubin rises above 4 or in certain cases 3 mg. per 100 cc. The reliability of the method is stressed.

FROM THE AUTHOR'S SUMMARY.

INTRAVASCULAR RED CELL AGGREGATION IN NEWBORN INFANTS WITH INFECTIONS. T. ARAJARVI and H. ZILLIACUS, Acta pædiat. **41**:260 (May) 1952.

The blood stream can be directly observed in the conjunctival blood vessels with the aid of a steromicroscope at 40 to 100 times magnification. When this method of observation was applied in a large number of newborn infants during the first days or weeks of life, it was noted that the blood stream in the small vessels and capillaries of the conjunctiva was even and ungranulated in completely healthy children. The red blood cells flowed along in even, single, or double lines in both capillaries and paracapillaries. In the larger vessels the blood stream was even and

ungranulated. However, as soon as even very slight prodromal signs of infection appeared, such as a slight rise in the temperature, a lowering of the general condition, vomiting, or abnormality of the stools, the circulating red blood cells began to form into clumps. In many cases aggregation of the red blood cells was the first sign of infection to appear. The aggregating tendency was more pronounced when the infection was severe than when it was mild. The aggregation phenomenon was characterized by the fact that in capillaries and paracapillaries colorless spaces were observable between erythrocyte "carriages" of varying lengths. In vessels of larger caliber the blood stream was granulated. The rate of flow was decreased in all the vessels studied. As it is known from earlier investigations that the degree of red blood cell aggregation bears a certain relationship to the increased sedimentation rate of the red blood cells, intravascular aggregation in infants with infection may be regarded as a sedimentation reaction directly observed in vivo. Instead of using the microsedimentation reaction, an early diagnosis of infection can be made by direct observation of the blood stream with a view to detecting the possible presence of red blood cell aggregation. This also holds good for premature babies. Cases of erythroblastosis fetalis and cases with extensive traumatic lesions (for example, parturation injuries) form exceptions to this rule, since they also display intravascular red blood cell aggregation. Fifteen cases are described.

FROM THE AUTHORS' SUMMARY.

INTRAVASCULAR RED CELL AGGREGATION IN ERYTHROBLASTOSIS FETALIS. H. ZILLICAS and T. ARAJARVI, Acta pædiat. **41**:267 (May) 1952.

The blood stream in the small conjunctival vessels was observed in 12 cases of erythroblastosis fetalis with the aid of a stereoscopic microscope immediately after birth. Intravascular red blood cell aggregation was observed in all the immunized infants. No aggregation was observed in healthy newborn infants. The correlation between the blood values in the child and the degree of aggregation was such that, when the aggregation was pronounced, the red blood cell and hemoglobin values were low. After a blood exchange or in connection with a spontaneous improvement in the state of health, the red blood cell aggregation decreased proportionally as the blood values improved.

The diagnostic and clinical significance of these observations is discussed.

FROM THE AUTHORS' SUMMARY.

DIAPHRAGMATIC HERNIA AS A CAUSE OF ASPHYXIA IN THE NEWBORN. TUOMAN PELTONEN, Acta pædiat. **41**:527 (Nov.) 1952.

Four cases of congenital diaphragmatic hernia are reported, three occurring on the left side and one on the right side; the symptoms and the differential diagnosis are discussed. In associaiton with diaphragmatic hernia, other abnormalities have been found, and therefore the author feels that this abnormality arises about the second month of fetal life. It is important for the pediatrician to make an early diagnosis, in order that the condition can be dealt with surgically.

FROM THE AUTHOR'S SUMMARY.

TREATMENT OF NEWBORN INFANTS OF RH-IMMUNIZED WOMEN. BIRGER BROMAN, Nord. med. **46**:1091 (July) 1951.

A review of the various measures used hitherto is presented. The author reports 41 consecutive cases of live-born Rh-positive babies born to Rh-negative and Rh-immunized women. Thirty-four of the infants were given exchange transfusion. Two of the 41 babies died. The 39 surviving babies showed no sign of brain injury during the neonatal period or later.

WALLGREN, Stockholm, Sweden.

NEWBORN WITH ENDOTHELIOMA OF THE NECK AND THROMBOPENIA. A. G. SCHOO, Maandschr. kindergeneeskunde. **20**:388 (Dec.) 1952.

Clinical description of a fatal case in a neonate with a large hemangioendothelioma in the neck and thrombocytopenic purpura. The bone marrow was normal. Four cases of angioma or hemangioendothelioma are quoted from the literature. X-ray irradiation may lead to recovery, with disappearance of the tumor and regulation of the number of thrombocytes.

FROM THE AUTHOR'S SUMMARY.

Acute Contagious Diseases

PRESENT CONCEPTS AND RECENT ADVANCES IN ACUTE POLIOMYELITIS. J. R. PAUL, A. M. A. Arch. Int. Med. **90**:271 (Aug.) 1952.

Recent advances in knowledge of the pathogenesis and epidemiology of poliomyelitis are presented and discussed.

Of primary importance is the demonstration by Enders and co-workers, that poliomyelitis viruses may be grown in non-nervous tissue cultures. This is consistent with the recent isolation by Wenner of virus from the lymph nodes of human cases. Ward and co-workers have demonstrated a short period of viremia during the incubation period of the disease in humans.

The importance of tissue culture in experiments on virus isolation, neutralization, and typing is emphasized. Also discussed are the various immunologic species of poliomyelitis virus and the associated problems of immunization.

The lack of success in controlling epidemics by both sanitary control and immunization methods is cited. The results of the attempts to produce passive-active immunity with gamma globulin are not covered in this review.

ETTINGER, Chicago.

MYOSITIS OSSIFICANS OCCURRING IN POLIOMYELITIS: REPORT OF A CASE. W. E. HESS, A. M. A. Arch. Neurol. & Psychiat. **66**:606 (Nov.) 1951.

After fracture of the femoral shaft during physical therapy four months after onset of poliomyelitis, x-rays revealed calcification of the thighs. After immobilization for the fracture, this calcification increased. The author concludes that the trauma of stretching the muscles may be responsible for the myositis.

MCGUIGAN, Evanston, Ill.

ABSENCE OF CLINICAL EVIDENCE OF DESTRUCTIVE LESIONS OF THE SYMPATHETIC NERVOUS SYSTEM IN ACUTE ANTERIOR POLIOMYELITIS. LEWIS T. POLLOCK, NORMAN B. DOBIN, BENJAMIN BOSHES, ALEX J. ARIEFF, HERMAN CHOR, I. FINKELMAN, MEYER BROWN, IRVING C. SHERMAN, ERICH LIEBERT, and ELI L. TIGAY, A. M. A. Arch. Neurol. & Psychiat. **67**:725 (June) 1952.

Intensive examination of patients with acute paralytic poliomyelitis failed to reveal any clinical evidence of destruction of function of the sympathetic nervous system.

MCGUIGAN, Evanston, Ill.

NOR-EPINEPHRINE IN THE TREATMENT OF ACUTE MENINGOCOCCEMIA WITH SHOCK (WATERHOUSE-FRIDERICHSEN SYNDROME) AND AN EVALUATION OF ADRENOCORTICAL FUNCTION. HENRY S. M. UHL, New England J. Med. **249**:229 (Aug.) 1953.

The author describes a classic case of the Waterhouse-Friderichsen syndrome in which intravenous infusion of arterenol (nor-epinephrine) was carried out during the first 60 hours to combat circulatory collapse and to maintain a normal blood pressure.

Studies on adrenocortical function during the acute phase of the illness and after recovery indicated no failure of the adrenal cortex. The syndrome of shock did not respond, moreover, to parenteral adrenocortical replacement therapy.

The author believes that the use of a continuous infusion of arterenol maintained a normal blood pressure and prevented irreversible shock and serious renal damage from ischemia.

WHEELOCK, Denver.

CYSTITIS AND MENINGOCOCCIC INFECTION. F. CORRIAS, Ann. ital. pediat. **5**:309 (Aug.) 1952.

The author reports two cases of meningococcic meningitis with contemporary cystitis.

After pointing out the extreme rarity of cystitis complications in the meningococcic infection, the author presents some possible pathogenetic interpretations.

FROM THE AUTHOR'S SUMMARY.

PURULENT SUBDURAL HYGROMA FOLLOWING A CASE OF MENINGOCOCCIC MENINGITIS. THOMAS SALA SANCHEZ and JOAQUIN COLOMER SALA, Acta pediat. españ. **10**:383 (June) 1952.

This is a case of subdural hygroma which followed meningococcic meningitis in a child of 14 months. There had been prolonged intrathecal treatment of the meningitis. The author says it is the first case of this type he has seen among many treated in like manner with penicillin or sulfonamides, although many American writers have commented on subdural complications after prolonged intrathecal treatment. The surgical procedure is described. X-ray of skull showing the mass of fluid and a photograph of the child are included. After drainage, the postoperative course was eventful, and the child made a good recovery without sequelae.

The differential diagnosis is discussed, as well as the anatomical aspects of subdural lesions in infancy.

ALLEN, San Francisco.

EPIDEMIOLOGY AND DIAGNOSIS OF POLIOMYELITIS. J. VALL BONARES, Arch. pediat. **1**:55 (July) 1950.

This is an outline of the known facts and the mystifying unknowns in the epidemiology of poliomyelitis. This includes the nature of the virus, its physical and chemical properties, and its resistance. The fact is mentioned that oxidizing agents and ultraviolet rays do destroy the virus.

It is specifically neurotropic but is found in feces and nasopharyngeal secretions, even in some healthy persons. There is no known animal reservoir between outbreaks of epidemics. The human being is the only interepidemic reservoir.

It is transmitted by water and has been isolated from raw vegetables and from the feet of flies, and there is question about the means of direct transmission, whether by droplets of secretions in the air, direct contacts, or by food handling. Although indications are that water supply is the big factor, the others cannot be totally ignored.

Portals of entry are nasopharyngeal, intestinal, mucosal; why it selects in one case the anterior horn cells in the cord and in other cases the bulb is not clear, nor is the means of travel clear, but this latter is probably by blood and lymphatic circulation.

The period of incubation is discussed, as well as susceptibility and immunity. The gradual shifting of the greatest number of cases from infancy to young adulthood is mentioned.

The late summer and autumn is the time of the greatest number of cases, and, although found more in the temperate zones of the earth, it is present to less extent in all geographical areas.

Under diagnosis the abortive, nonparalytic, and paralytic forms are described from a clinical point of view. The spinal fluid examination is the only practical laboratory procedure which will be of any help in diagnosis.

For early diagnosis the author puts great reliance on "sign of the tripod," in which the child, when asked to sit up in bed, holds his back and neck very stiff and supports himself with his arms in the manner of a tripod. Also, flexion of the back to touch the knees is quite painful. This may occur before any other signs. The muscle spasm and later paralysis are described.

The paralysis affecting the respiration, both peripheral and due to invasion of the respiratory center, are described. Symptoms of pharyngeal and soft palate paralysis are described.

Differential diagnosis and some of the rarer forms of poliomyelitis, such as the leptomeningeal and the encephalitic forms, conclude the paper.

ALLEN, San Francisco.

NODULAR RADIOGRAPHIC INFILTRATION IN MEASLES. A. INVALDI and E. N. RAZZETTE, Arch. argent. pediat. **37**:28 (Jan.-Feb.) 1952.

In 54% of 115 cases of typical rubeola, roentgenograms of the lungs were abnormal. Changes appeared on the second day of the eruption and were characterized by disseminated nodular opacities, varying in number and density. These were consistently accompanied by marked hilar reaction. The changes persisted after clinical recovery, lasting 15 to 30 days. The picture is that of interstitial pneumonitis seen in other viral diseases. There is no relationship between severity of clinical signs and symptoms and the roentgenographic changes.

PANOS, Galveston, Texas.

THE USE OF NEBULIZED ANTIBIOTICS IN THE TREATMENT OF WHOOPING COUGH. ALBERTO CHATTAS, Arch. argent. pediat. **37**:127 (April) 1952.

Chloramphenicol (Chloromycetin), chlortetracycline (Aureomycin), and oxytetracycline (Terramycin) were administered orally and by nebulization in 15, 10, and 15 cases of whooping cough, respectively. Nasopharyngeal cultures became negative within three to five days, and the average time required for "cure" was approximately five days.

PANOS, Galveston, Texas.

WHOOPING COUGH TREATED WITH AUREOMYCIN. WERNER E. BUSTAMANTE, Rev. chilena pediat. **21**:77 (Feb.) 1950.

Two cases of whooping cough treated with chlortetracycline (Aureomycin) are reported. The drug was given with a dosage of 20 and 30 mg. per kilogram of body weight every 24 hours, divided into four equal doses during a week. Chlortetracycline appears to improve markedly the clinical course of whooping cough after the third day of treatment. No toxic or side reaction was present.

FROM THE AUTHOR'S SUMMARY.

THE TREATMENT OF POLIOMYELITIS. F. FORMIGAL LUZES, Arq. pediat. **24**:275 (May) 1952.

A review of the literature, with a discussion of each type of treatment that has been proposed for poliomyelitis, is presented. The conclusions state that physical therapy adapted to the particular case, with orthopedic assistance, has proved to be the best form of treatment, though far from ideal.

CHRISTOPHERSON, San Diego, Calif.

SECOND ATTACKS OF SCARLET FEVER. ERICH NÜBEL, Deutsche med. Wchnschr. **78**:1189 (Aug. 28) 1953.

The incidence of second attacks of scarlet fever months or years after the first attack is given in the literature as 0.06 to 2.7%. During an epidemic, 3,479 patients with cases of scarlet fever were observed. Of these, 55, that is, 1.58%, probably had second attacks. Thirty of these children (0.86%) were seen during both attacks. The shortest time interval was 3 months, the longest, 13 years. In 22 of the 30 cases, the first attack occurred before the age of 6 years.

AMBERG, Rochester, Minn.

PRESENT TREATMENT OF SCARLET FEVER. KARLA WEISSE, Med. Klin. **48**:1111 (July 31) 1953.

Weisse reports that scarlet fever patients should receive penicillin treatment early and with sufficient dosage. The patient should be removed from the scarlet fever ward early. The author recommends removal on the fifth day with penicillin protection. As a rule, when under proper penicillin treatment, streptococci have disappeared from the throat, and the danger of contagion no longer exists. If the patient has no further symptoms, dismissal to the home is recommended. If the patient is to be regarded clinically ill, owing to the severity of the attack, he is dismissed from the scarlet fever ward to another part of the hospital. Reentrance to school is permitted sooner than the previously demanded six weeks on permission of the physician. It is further recommended to keep the scarlet fever patient in rooms with one to three beds, since the "usual" scarlet fever wards harbor streptococci of all groups and types, favoring complications, recurrences, and spreading of the disease on dismissal to the home. The problem of possible interference of penicillin treatment with development of immunity is not definitely solved as yet. The author emphasizes that his experience is limited, inasmuch as the recent epidemics of scarlet fever have been light.

AMBERG, Rochester, Minn.

A NEW TREATMENT OF PERTUSSIS. H. PANTLEN, Med. Klin. **48**:1223 (Aug. 21) 1953.

A secretion from snails has been used in folk medicine against bronchial troubles. A preparation from such secretions of pulmonate snails obtainable commercially was used in cases of pertussis, in some cases with surprising benefit.

AMBERG, Rochester, Minn.

THROMBOCYTOPENIC PURPURA AFTER MORBILLI. MOHAMAD ATTA and BENGT SIEVERT, Acta pædiat. **42**:364 (July) 1953.

The authors report a case of thrombocytopenic purpura after morbilli in a girl 9 years old, previously healthy. On the 10th day after the appearance of the morbillous exanthem, cutaneous and mucous membrane hemorrhages with an increasing intensity were noted. On hospitalization, she had thrombocytopenia and a prolonged bleeding time. She lost large amounts of blood, which were replaced by repeated blood transfusions. The hemorrhages began to abate after 12 days. The patient was discharged after a month. The subsequent follow-up period was uneventful except for a moderate persistent thrombocytopenia. A brief comparison is made between the present case and four earlier ones. A discussion of the genesis, therapy, and prognosis of the disease is included.

FROM THE AUTHORS' SUMMARY.

RUBELLA DURING PREGNANCY. ROLF LUNDSTROM, Acta pædiat. **41**:583 (Nov.) 1952.

An investigation has been started to ascertain the pathogenic effects on the fetus in a case of rubella in the mother during pregnancy. A preliminary report is given to these effects, as assessed at birth and shortly afterwards, in a series of 1,067 cases of rubella during pregnancy.

Rubella during the first 4 months of pregnancy is found to have a demonstrable effect in the form of stillbirth, neonatal death, anatomically demonstrable abnormalities, and immaturity. The total incidence is approximately 17% as compared to approximately 6% in a concurrent control series.

A higher incidence (11%) of abnormal fetuses than in the controls is also recorded in the following group: Women who had earlier suffered from rubella had been exposed to infection by the virus during the first 4 months of pregnancy and had not contracted rubella on this occasion.

Women who had not had rubella earlier and who were known to have been in contact with rubella during their pregnancy but did not contract the disease show a slightly higher incidence (approximately 7%) of abnormal fetuses than the control series. This difference is not significant.

After the fifth month of pregnancy, neither an attack of rubella nor exposure to the infection without contracting it is found to result in any significant difference as compared to the control series.

The investigation is being continued with regard to both the further development of children and the results of the administration of convalescent serum.

FROM THE AUTHOR'S SUMMARY.

Acute Infectious Diseases

RESULTS OF CORTISONE-CORTICOTROPIN THERAPY IN CHRONIC ACTIVE RHEUMATIC FEVER. D. YOUNG and M. ROBSTEIN, A. M. A. Arch. Int. Med. **90**:64 (July) 1952.

Eight children with chronic active rheumatic fever, ranging in age from 8 to 16 years, were treated for prolonged periods with cortisone or corticotropin. Two of the patients recovered and remained free of rheumatic activity during a prolonged period of observation. Four of the patients continued to have active disease, and in one other the process was reactivated after two weeks' quiescence. One patient died with congestive failure during 35 days of cortisone therapy.

Most patients observed a sense of well-being and a loss of fever unassociated with the degree of actual clinical improvement. There were no striking effects on the various manifestations of carditis. In contrast to the effects observed in acute rheumatic fever, laboratory improvement was not marked. Side-effects, such as gynecomastia, hirsutism, striae, and hypertension, were noted. In one 12-year-old boy there developed massive gastrointestinal bleeding from duodenal ulceration.

The authors feel that the severity of the disease was diminished in four of the patients and terminated in one by this therapy. Congestive heart failure, previously resistant to therapy, cleared in four of five patients. The authors conclude that in some children with severe chronic active rheumatic fever prolonged administration of large doses of cortisone or corticotropin may be life-saving.

ETTINGER, Chicago.

PRESENT STATUS OF DIAGNOSTIC TESTS FOR RHEUMATIC FEVER. M. MCCARTY, Ann. Int. Med. **37**:1027 (NOV.) 1952.

Two groups of tests are currently in use for the diagnosis of active rheumatic fever. The first is concerned with the measurement of antibody against certain of the products of Group A streptococci. Although positive evidence of a recent streptococcal infection in most cases does not indicate rheumatic fever, the ability to demonstrate recent infection may often help to clarify a confusing clinical picture. The method of Todd for the measurement of antistreptolysin O is simple, reproducible, and usually reliable. Determinations of streptokinase and streptococcal hyaluronidase are less generally adaptable. In 46 consecutive cases of early rheumatic fever, the mean titer of antistreptolysin O was 500 units per cubic centimeter. The very young children in this group showed the lowest titers. Only one-fourth of the cases had unequivocal positive results, but others by serial determination showed such rapidly falling titers that they were presumed positive.

The second group, comprising nonspecific procedures, is actually less diagnostic tests than indicators of rheumatic activity. These include the erythrocyte sedimentation rate, the leucocyte count, and the determination of C-reactive protein. These, perhaps, have their greatest diagnostic value when negative, since they are so consistently positive in cause of acute rheumatic fever that a normal reaction is strong evidence against the diagnosis.

ETTINGER, Chicago.

EOSINOPHILIA IN CHILDHOOD CAUSED BY VISCERAL LARVA MIGRANS. JOHN H. DENT and G. M. CARRERA, J. Louisiana M. Soc. **105**:275 (July) 1953.

Eosinophilia in childhood not accounted for by other causes may be a sign of visceral larva migrans caused by some species of nematode normally present in lower animals. Specific diagnosis cannot be made by stool examination, since these worms do not complete their life cycle in man. Liver biopsy is at present the only means of establishing the diagnosis.

MCGUIGAN, Evanston, Ill.

TREATMENT WITH AUREOMYCIN OF LOCALIZED PASTEURELLA MULTOCIDA INFECTION. ERWIN NETER, E. HOYT DEKLEINE, and RICHARD W. EGAN, J. Pediat. **38**:242-243 (Feb.) 1951.

Chlortetracycline (Aureomycin) successfully healed a chronic infection of the nose caused by Past. multocida. Treatment was local and peroral.

MACDONALD, Pittsburgh.

CLINICAL EVALUATION OF STREPTOMYCIN IN THE TREATMENT OF BACILLARY DYSENTERY IN INFANCY AND CHILDHOOD. S. Y. CHANG and T. F. SU, J. Pediat. **38**:602-609 (April) 1951.

The authors studied 130 cases of Shigella dysentery in infants and children with positive stool cultures. Organisms identified in 122 cases of Shigella Flexner included 120 cases of Flexner Type II (Boyd's Type II), 3 cases of S. sigae, 4 cases of S. anbigua, and 1 case of S. sonnei. Streptomycin was given in doses of 60 to 80 mg. per kilogram per day divided into six doses orally, plus 40 mg. per kilogram per day divided into two, four, or six doses parenterally. Fluid therapy and supportive measures were used when indicated. Response to streptomycin was prompt and permanent in about 96% of the children. Sulfonamide therapy was definitely less successful.

MACDONALD, Pittsburgh.

LABORATORY DIAGNOSIS OF VIRUS AND RICKETTSIAL INFECTIONS. J. A. DUDGEON, J. Great Ormond St. **1**:3-21 (June) 1951.

The role of the virus laboratory in the diagnosis of disease is discussed. Methods used in the laboratory are presented in some detail. Diagnostic tests are available for 19 different specific infections by viruses and Rickettsia. A table is included showing the material required and how it is collected for each disease. Methods of virus isolation are described,

including cultural as well as serological tests and tissue studies. It is pointed out that the function of a virus diagnostic laboratory is to provide facilities for diagnosis and also to assist in the investigation of disease.

The article does not lend itself to abstracting but should be read by all those interested in methods of investigation of virus diseases. McGuigan, Evanston, Ill.

Active Immunization Against Tetanus. E. A. North and R. W. Patterson, M. J. Australia, **1**:797 (June 6) 1953.

Routine immunization against tetanus plus a stimulating dose 12 months later may give protective antibody levels for as long as eight or nine years. Stimulating doses are recommended at five-year intervals, as well as after injury. McGuigan, Evanston, Ill.

Regional Non-Bacterial Suppurative Lymphadenitis and Its Relationship to "Cat-Scratch Disease." J. I. Tonge, J. A. Inglis, and H. E. Derrick, M. J. Australia **2**:81 July 18) 1953.

Sixteen cases of regional suppurative lymphadenitis following bites or scratches by cats were described in Queensland. While most of these cases are benign, one patient died of encephalitis presumably caused by the same virus. McGuigan, Evanston, Ill.

A Problem of Infectious Diseases. R. V. Sanzgiri, Indian J. Child Health **1**:562-566 (Nov.) 1952.

The need for universal immunization against smallpox, whooping cough, and diphtheria is again emphasized. The author pleads for wider recognition of the fact that prevention of disease is the function of all physicians; not only of the State Health Departments.

McGuigan, Evanston, Ill.

Kwashiorkor in Africa. J. F. Brock and M. Autret, South African M. J. **26**:737-739 (Sept. 13) 1952.

The authors, who have previously published an exhaustive treatise on kwashiorkor in Africa, present here a very brief statement of the nature of the disease, with suggestions as to treatment, prevention, and subjects for further investigation. McGuigan, Evanston, Ill.

Negative Cercarial Antigen Skin Tests in Proved Urinary Bilharziasis in Children. H. I. Lurie, B. De Meillon, N. Stoffberg, and H. H. Eiselen, South African M. J. **27**:295 (April 11) 1953.

The authors found negative skin test reactions in 24 of 27 children suffering from proved bilharziasis. They conclude that the skin test is not to be relied on in children.

McGuigan, Evanston, Ill.

Hyperventilation in Toxicosis in Grippe in Infants. E. Kerpel-Fronius, F. Varga, K. Kun, and J. Vönöczky, Ann. pædiat. **177**:1 (July) 1951.

Toxicosis with hyperventilation following infection presents a clinical picture characterized by coma, hyperventilation, and acetonemia in which diarrhea and vomiting are of slighter importance.

The blood circulation time is hardly prolonged; dehydration—without salt depletion—appears to be only secondary and due to increased water loss in the lungs. In the blood the significant findings are the reduction of the arteriovenous (sinus blood) O_2 and CO_2 differences, the high degree of acapnia, the hyperchloremia, the acetonemia, and the slight degree of blood concentration. From the Author's Summary.

OBSERVATIONS ON FIFTY-SIX CASES OF TYPHOID FEVER TREATED WITH VACCINE AND CHLORAMPHENICOL. G. ZAULI NALDI and L. GASPARRONI, Clin. pediat. **35**:253 (April) 1953.

Over a 16-month period at a hospital in Teramo, 56 children, 43 with typhoid fever and 13 with paratyphoid fever, were routinely treated by injections of a vaccine (Anazifo Sclavo). The vaccine was usually given intravenously, but sometimes intramuscularly. No untoward hyperpyrexia resulted from the vaccinal therapy. Several of the patients with more severe cases were also given chloramphenicol. Four of the patients died.

HIGGINS, Boston.

A CASE OF BENIGN INFECTIOUS LYMPHORETICULOSIS: CAT-SCRATCH FEVER. G. CHIARI, Lattante **23**:158 (March) 1952.

A 3-year-old boy had been playing with cats and had been frequently scratched by them. His illness began with appearance on the left side of his neck of a small lesion which healed in a short time. Eight days later there began an enlargement of three lymph nodes just above the left clavicle. One week later the boy began to have fever and was sick. A tuberculin test and a Wassermann test were done and were negative. One of the nodes became much larger, red, and tense. Aspiration of this node yielded about 1 cc. of pus greenish-yellow in color. Microscopic examination of the pus showed no bacteria, much cellular detritus, and some lymphocytes and granulocytes. Recovery was rather rapid. It was suspected that the child had cat-scratch fever (benign infectious lymphoreticulosis of Debré). The blood counts had been essentially normal. The disease is believed to be caused by a virus. Skin tests with material obtained from Debré's laboratory in Paris were positive. This is the first case reported in Italy. Cases in the United States have been reported by Foshay and by Greer and Keefer.

HIGGINS, Boston.

PHYSIO-PATHOLOGY OF IMMUNITY IN CHILDREN. F. S. MARTINEZ, Minerva pediat. **4**:175 (March 15) 1952.

The various factors which influence the development of immunity in children, including heredity, age, allergy, weather, and antibiotics, are considered.

HIGGINS, Boston.

ARTHRITIS FROM SALMONELLA TYPHIMURIUM. G. ROSSI, Minerva pediat. **4**:465 (June 15) 1952.

The cases are reported of two infants, each one and one-half months old, with Salmonella typhimurium infections. One child had a meningitis followed by a knee infection; the Salmonella organisms were recovered from the feces, the spinal fluid, and the fluid aspirated from the knee. Treatment was with streptomycin and chloramphenicol. The other infant had arthritis involving several joints; this disease appeared first in a knee and subsequently in each shoulder joint. Treatment was with sulfathiazole, streptomycin, and penicillin. Both infants recovered completely, although their illnesses were rather long.

HIGGINS, Boston.

THE MECHANISM OF THE ACTION OF SODIUM SALICYLATE IN ANTIRHEUMATIC THERAPY. U. PELLEGRINI and I. SALA, Pediatria **61**:351 (May) 1953.

Each of seven children were given 4 cc. (1.2 gm.) of a 30% solution of sodium salicylate in distilled water intravenously. In another group of seven children, each child was given 0.2 gm. sodium salicylate per kilogram of body weight in divided doses by mouth daily for four days. Each child showed a marked diminution in the number of eosinophile cells in the blood (average 54%) and an increase in the amounts of 17-ketosteroids and 11-oxysteroids excreted in the urine. These results suggest that the therapeutic action of sodium salicylate is through the adrenal cortex.

HIGGINS, Boston.

PECULIAR EVOLUTION OF A CASE OF PARATYPHOID B IN A CHILD OF SEVEN YEARS. ROANO POSSI, Riv. clin. pediat. **50**:414 (June) 1952.

A case is reported of congestive splenomegaly which occurred after an episode of paratyphoid B, cured by intense antibiotic treatment.

FROM THE AUTHOR'S SUMMARY.

EPIDEMIOLOGICAL AND THERAPEUTIC CONSIDERATIONS OF A TYPHOID EPIDEMIC AMONG CHILDREN. ENRIQUE GARRALON JORBA, Acta pediat. españ. **8**:801-814 (July) 1950.

In colorful language and with unusual humor Jorba describes an epidemic of typhoid in small isolated villages in the province of Zamora. This epidemic, which lasted from April until November, 1948, occurred before the Health Department started the routine use of chloramphenicol in typhoid fever cases.

Of the 43 patients, 17 were children; none of the children who became ill had been immunized against typhoid.

The physician goes into details about the epidemiological features: water supply, number of grazing livestock, method of disposal of human wastes, etc., and the fact that there had not been a case of typhoid in this area for 15 years. It was not considered an endemic area for this disease, and bacteriological examination revealed sources of water as "potable."

The first patient was the only baker in one of the villages. He was isolated and instructed in methods of dealing with wastes and methods of handling food. During an entire month no cases developed, although the villagers ate the baker's bread which had been transported without permission to the plaza. In fact, the whole spread of the disease could be laid to the flies which hatched out in May, and the cases did not stop developing until fall when the flies were killed by frost. The author quotes Hamilton, of Chicago, in saying that a contaminated fly may travel by train or car and start an epidemic where milk and water supplies are excellent.

Dr. Jorba gives details of the poor hygienic conditions which help the fly in its nefarious work. D.D.T. may kill the adult flies, but if some method is not used to destroy larvae, the spread continues. He describes the Millar trap for the destruction of larvae and concludes that if manure and human wastes were collected promptly and properly treated the country would be surprised at the fall in typhoid rates and the rapid reduction of infant mortality.

He also says that although it is illegal to kill the carrier it is not so in the case of the fly.

The high percentage of children contracting the disease could be blamed on poor hygiene and on the village pastime of fly catching as well as on the preference the flies showed for children.

The diet during treatment in children was almost wholly liquid, with absolute deprivation of any fats. Nasal tube feeding of dextrose and amino acids was routine in many of the gravely ill children. Tea and vitamin B preparations were given, and when the diarrhea was controlled milk was added. Later when the diarrhea was less copious, fruit juices were added and freshly prepared meat extracts.

The physician did not use any of the bismuth preparations, as he does not believe they are well tolerated by children. Since chloramphenicol was not available, aminopyrine was used and suprarenal cortex preparations for circulatory collapse.

The dosage of aminopyrine was 1 cg. daily for each year of age until 6 years; then 15 to 20 cg. was given daily, with a day without drugs after each three days of medication.

The physician was unable to make any blood studies to determine if there were any resulting agranulocytosis, but the side-effect of deafness or tinnitus disappeared as soon as the drug was discontinued.

Only one child died in the epidemic, and in his case peritonitis followed perforation of the small intestine.

Allen, San Francisco.

A CASE OF TETANUS NEONATORUM, WITH RECOVERY TREATMENT WITH SPECIFIC ANTITOXIN AND PENICILLIN. JESUS MARTINEZ FERNANDEZ, Acta pediat. españ. **10**:227-230 (Feb.) 1952.

A case of tetanus in a newborn was seen by the author on the eighth day after birth. The cord was off, but the area around the umbilicus showed evidence of infection, and the child had all classical signs of tetanus.

Treatment consisted of feeding dextrose by nasal catheter and administering 25,000 units of tetanus antitoxin intramuscularly daily, 200,000 units of penicillin every 8 hours, and 5 cc. of phenobarbital sodium every 12 hours.

Oxidizing agents were used locally, and by the fourth day the symptoms had entirely disappeared. Recovery of weight and subsequent progress have been good.

The author outlines the differential diagnosis.

ALLEN, San Francisco.

TREATMENT OF TYPHOID WITH TERRAMYCIN. OSCAR UNDURRAGA, ALFREDO RAIMANN, and JULIO MENEGHELLO, Rev. chilena pediat. **23**:306 (July) 1952.

The authors report their experience with oxytetracycline (Terramycin) in 17 cases of typhoid of more than seven days' duration. The drug was administered orally in a dose of 100 mg. per kilogram per day given every six hours for 12 days. In seven patients the results, judged by the drop in temperature and the improvement in their general condition, were considered good. In the other 10 patients treatment failed owing to intolerance to the drug as manifested by persistent vomiting or owing to the persistence of fever. The authors believe their results are comparatively inferior to those obtained with chloramphenicol.

FROM THE AUTHORS' SUMMARY.

A FEW CONSIDERATIONS ON THE PATHOGENESIS OF BRUCELLOSIS CLINICAL CASES TREATED WITH OXYTETRACYCLINE (TERRAMYCIN). FERNANDO LOPEZ CLARES and ADRIAN PEREZ RAMIREZ, Bol. méd. Hosp. inf. **10**:160 (April) 1953.

In the pathogenesis of brucellosis, a very important role is played by the intracellular parasitism of Brucella. This peculiar form of parasitism renders very difficult the entrance of microbiotic influence, hypersensitizes the host, and allows a periodic discharge of germs.

Thirteen cases of brucellosis were treated with oxytetracycline (Terramycin). The doses were between 50 and 100 mg. per kilogram of body weight per day for 10 consecutive days, 14 days in one case.

There was a definite and quick improvement of symptoms, but there were four relapses out of nine cases under control. The drug was well tolerated in every case. The results are similar to those previously found by other authors using the same drug.

FROM THE AUTHORS' SUMMARY.

AMEBIASIS WITH INTESTINAL PERFORATION AND PERITONITIS. MAXIMILIANO SALAS MARTINEZ, ERNESTO CONTRERAS RODRIGUEZ, JULIO CARRILLO RASCON, JESUS VILLEGAS GONZALEZ, GUSTAVO LOPEZ POUMIAN, and GUSTIN BARRERA, Bol. méd. Hosp. inf. **10**:177 (April) 1953.

Presentation is made of a case of amebic ulcerative colitis in a baby girl 1½ years of age. The process caused microscopic abscesses in the liver followed by intestinal perforation caused by peritonitis. Thrombosis of the upper longitudinal sinus appeared followed by a hemorrhagic bronchopneumonia of bacterial nature as a final stage. In the final comments, the authors stress the frequency of amebiasis in Mexico and the necessity to keep this frequency in mind when differential diagnoses are made in infectious diarrhea in children.

FROM THE AUTHORS' SUMMARY.

IS IT POSSIBLE TO RENDER TAPEWORM THERAPY FREE OF DANGER? R. SCHOEN and H. H. SCHNEIDER, Deutsche med. Wchnschr. **78**:1057 (July 31) 1953.

The authors report two deaths of adults due to faulty medication for tapeworm infestation. They recommend administration of acridine or a similar product, Acranil, in solution by means of a tube introduced far into the upper jejunum to reach in sufficient concentration the head of Taenia saginata, which is anchored there. In the adult 0.8 gm. quinacrine hydrochloride (Atabrine) dissolved in 80 ml. of water was used, followed in half an hour by a solution of magnesium sulfate by the tube. Phenobarbital (Luminal) or atropine may be used to combat vomiting. No trials are reported in children.

AMBERG, Rochester, Minn.

PERFORATION OF THE GALL BLADDER AS COMPLICATION OF TYPHOID IN A CHILD. K. KLEIN, Med. Klin. **47**:934 (July 11) 1952.

An infant 4 months of age became ill with typhoid. Signs of perforation of an intestinal ulcer prompted a laparotomy. No perforation could be found; neither did the gall bladder present signs of any lesion. Six days later renewed signs appeared mainly in the region of the gall bladder. A small perforation of the gall bladder was found, and, there was a diffuse bile peritonitis. The infant died. The rarity of this complication of typhoid fever is stressed.

AMBERG, Rochester, Minn.

A DIAGNOSTICALLY IMPORTANT SYMPTOM OF PFEIFFER'S GLANDULAR FEVER. V. TOBIASCH and H. HORNER, Med. Klin. **47**:1048 (Aug. 15) 1952.

Attention is called to the appearance of small punctate hemorrhages in cases of infectious mononucleosis in the mucosa of the mouth. They were seen in 39 of 45 patients, all with acute tonsillitis, together with pharyngitis in some cases. Their occurrence speaks against a common angina and in favor of infectious mononucleosis, to be verified by further investigation.

AMBERG, Rochester, Minn.

SALMONELLA BOVIS MORBIFICANS INFECTION IN INFANTS. B. EPSTEIN, L. ZEMAN, and J. LEKSA, Pediat. listy **7**:197, 1952.

An institutional epidemic due to Salmonella bovis morbificans is described. A total of seven infants, aged 1 to 6 months, became ill; of these six were infected in the hospital. The illness manifested itself as an acute hemorrhagic enterocolitis. The contrast between the severity of the diarrhea and the comparatively slight alteration in general condition was striking. The organism was cultured from the stools and in one case from the urine. Blood cultures were negative. In four cases nonspecific type antibodies were demonstrated in the blood.

Treatment with chemotherapy, antibiotics, blood transfusion, and diet was successful. All the infants recovered. An institutional analysis of the epidemiology of the infection was attempted, and measures were taken which enabled the authors to overcome the infection with success.

FROM THE AUTHORS' SUMMARY.

Chronic Infectious Diseases

CONGENITAL SYPHILIS IN MASSACHUSETTS. NICHOLAS J. FIUMARA, New England J. Med. **245**:634 (Oct. 25) 1951.

The author's summary and recommendations are herewith printed in their entirety.

This article analyzes 59 cases of congenital syphilis among children born during the period 1946 through 1950 in order to determine reasons for the persistence of the condition in Massachusetts and to suggest control measures.

These children were about equally divided as far as sex was concerned. Numerically there were more white than Negro infants, but the number of Negro children born with congenital syphilis was higher than expected on the basis of white and Negro population distributions in the state.

Approximately 85% of the mothers were married. About 12% were single; this percentage of single mothers is probably higher than expectancy for the general population of Massachusetts.

Again, 13.6% of the mothers with syphilitic children were delivered at home, in contrast to the less than 2% of home deliveries for this length of time for mothers in the general population.

Congenital syphilis occurred because of the following factors.

Ignorance and carelessness of the mothers in not seeking prenatal care were responsible in 30% of the cases.

Approximately 20% of the mothers with prenatal syphilis received no treatment at all, because they failed to return to the physician's office. Approximately one-half of the mothers who did have prenatal care (adequate or inadequate) made their first appearance at the physician's office during the last trimester.

Inadequate treatment of the mother accounted for an additional 17% in this series of infected babies. Failure of the mother to return regularly to the physician for completion of scheduled treatment was the reason for the inadequacy of treatment.

Infection of the mother subsequent to the initial negative blood test was the cause of congenital syphilis in an additional 12% of the cases.

Relapse or more probably reinfection was the cause of congenital syphilis in another 5%.

Treatment failure appeared as the reason for congenital syphilis in 3% of these cases. However, treatment was given late in pregnancy, and the completion of treatment coincided with the onset of labor.

Inadequate basis for diagnosis of congenital syphilis was believed to account for about 7% of the cases reported.

Failure on the part of the physician to take a blood test for syphilis was the reason for congenital syphilis in the remaining 5% in this series.

Although this series of cases is small, it is clear that remedial measures are needed. The following recommendations are therefore offered.

A blood test for syphilis should be performed on all new patients in a physician's office, in a clinic, or in a hospital.

Women adequately treated for syphilis and seronegative should have blood tests at least once in the first and second trimesters of pregnancy and monthly during the last trimester. At least two blood tests for syphilis—one early and the other late in pregnancy—should be made on all women known to have been sexually promiscuous, women having a history of any venereal disease, and single, divorced, or separated pregnant women.

Women who have been adequately treated for syphilis but are still seropositive should be re-treated with penicillin during each succeeding pregnancy.

Physicians and health workers must redouble their educational efforts to persuade mothers and potential mothers to seek early, adequate prenatal care.

Patients with positive prenatal serologic tests who neglect to return to the clinic or to the physician's office for diagnostic study and treatment should be referred to the Massachusetts Department of Public Health, Division of Venereal Diseases, for follow-up study if the physician or clinic workers have been unable to persuade them to return.

All patients infected with syphilis and the other venereal diseases should be questioned about contacts.

Hospital authorities admitting a patient in labor as a house-service case are required to take a blood test for syphilis unless they are satisfied that one has been taken during this pregnancy.

All cases of venereal disease should be reported by the physician—either with or without the patient's name. In either event, the information given is safeguarded by state law.

WHEELOCK, Denver

LEPROSY AMONG CHILDREN—A SOCIAL PROBLEM. N. FIGUEREDO, Indian J. Child Health **1**:575-580 (Nov.) 1952.

Leprosy among children presents a social problem of considerable magnitude. Diagnosis of an early stage of the disease results in ostracism of the child, and because of the stigma still attached to the disease parents are reluctant to allow their children to be examined. All patients in an early stage of leprosy should be institutionalized. This will permit adequate treatment and release after three to five years. In the meantime, education can be continued, and the schooling thus obtained is frequently of a better degree than is available in regular schools. Intensive social work by trained personnel is essential to deal with situations arising in the family after such a diagnosis and to help in rehabilitation of discharged patients.

McGUIGAN, Evanston, Ill.

A COMPARISON OF THE PROTECTIONS GIVEN DOGS BY VACCINES CONTAINING LIVING (BCG) AND DEAD (PETRAGAI'S ANATUBERCULIN) TUBERCLE BACILLI. G. SALVIOLI, A. DELGI ESPOSTI, and M. A. DINA, Clin. pediat. **34**:137 (March) 1952.

Ten groups of litter-mate puppies, 40 animals in all, were used in these observations as to the comparative value of vaccines containing living or dead tubercle bacilli. Varying quantities of vaccine were used and varying intervals established between the giving of the vaccine and the injection of live bacilli some weeks later. Unvaccinated animals were used as controls.

It was definitely shown that both types of vaccine induced modifications in the animals which impeded the pathological action of the tubercle bacilli, as shown by a fewer number of lesions found by x-ray and at autopsy.

The vaccines conferred a state of allergy and a persisting positive tuberculin test; usually some small shadows were shown in the lungs by x-ray following the vaccination; these shadows later disappeared. For the best protective results, there must be set up an active focus, a latent or evident tuberculous lesion, preferably associated with some adenopathy.

The pulmonary lesions in the animals receiving anatuberculin tended to be fibrotic and interstitial in character, and in the animals receiving BCG they were bronchopneumonic. The animals receiving the anatuberculin had a lower mortality rate.

The maximum protective power of the vaccine is reached sooner with BCG than with the anatuberculin. But the ultimate protection of the anatuberculin is equal to that of BCG.

HIGGINS, Boston.

ABSORPTION, DIFFUSION, AND ELIMINATION OF ISONICOTINIC ACID HYDRAZIDE IN THE HUMAN BODY. R. PACHIOLI, D. COPPINI, and O. OLIVI, Clin. pediat. **34**:497 (Aug.) 1952.

Comparative observations were made on the levels of isoniazid (isonicotinic acid hydrazide) in the blood and in the spinal fluid of normal children and of children with tuberculous meningitis after the drug had been given by mouth. A higher blood level was reached in the normal child than in the tuberculous child, but the elimination by the urine was more rapid in the normal child. The drug passed readily from the blood into the spinal fluid in both groups of children. When the drug was injected intrathecally, a high concentration in the spinal fluid was reached immediately but fell rapidly, so that after about four hours the concentration was no higher than when the drug had been given by mouth. Analytical methods are described for the quantitative determination of isoniazid in the blood, the spinal fluid, and the urine.

HIGGINS, Boston.

CONTROL STUDIES WITH ANATUBERCULIN IN CREMONA IN THE YEARS 1937 TO 1942. V. MARCONI, Clin. pediat. **34**:537 (Aug.) 1952.

Observations were made of 212 children in 65 families with exposure to tuberculosis; 77 of the children had been vaccinated by anatuberculin shortly after birth, while their 135 brothers and sisters had not been vaccinated. Clinical tuberculosis was found in 38.5% of the nonvaccinated children and in only 7.7% of the vaccinated children. The illness was generally severer and of longer duration in the nonvaccinated group. None in the vaccinated and two in the nonvaccinated group died of tuberculosis. There also seemed to be a para-immunization in the vaccinated group in that these children were less prone to other infections.

HIGGINS, Boston.

EFFECTS OF STREPTOMYCIN, OF THE HYDRAZIDE OF ISONICOTINIC ACID, AND OF A COMBINATION OF THE TWO ON THE ACTIVITY OF EXPERIMENTAL TUBERCULOSIS IN GUINEA PIGS. M. ORLANDELLI and P. NICOLAJ, Clin. pediat. **34**:625 (Oct.) 1952.

Forty-five guinea pigs were given intradermal injections of a moderately virulent strain of tubercle bacilli. One group of animals served as controls. Other groups received 15 daily injections of (1) streptomycin or (2) isoniazid (the hydrazide of isonicotinic acid) or (3) a combination of the two drugs, beginning 24 hours after the injection of the tubercle bacilli. The animals were killed on the 40th day.

The animals receiving streptomycin showed no early reaction to the drug, and only one-third of them showed any lymph node enlargement or caseation at autopsy.

The animals receiving isoniazid showed a local reaction (redness and edema) a few hours after the injections of the first few days. There was then a quiescent period until 15 days after the last injection; then a marked inflammation at the site of the tubercle bacilli injections and a swelling of the lymph nodes appeared. At autopsy, microscopic examination revealed extensive tuberculous activity and caseation at the site of the inoculations, in the lymph nodes, and in the abdominal organs in 90% of the animals.

When the two drugs were given together, the local reaction was the same as when isoniazid was given alone but was not of so long duration; although the clinical symptoms were not so marked, yet in 80% of the cases there was found at autopsy extensive lymph node and visceral involvement.

HIGGINS, Boston.

BLOOD SEDIMENTATION RATE IN CHILDREN UNDERGOING TREATMENT WITH STREPTOMYCIN FOR TUBERCULOUS MENINGITIS. B. CARLETTI and C. FUSARI, Minerva pediat. **4**:343, (May 15) 1952.

From a study of 81 children with tuberculous meningitis who were being treated with streptomycin, no definite correlation could be established between the clinical status of the patient and the blood sedimentation rate.

HIGGINS, Boston.

PRELIMINARY STUDIES ON THE INTRATHECAL ADMINISTRATION OF THE HYDRAZIDE OF ISONICOTINIC ACID IN ANIMALS AND HUMANS BY THE CISTERNAL AND THE LUMBAR ROUTES: FIRST IMPRESSIONS ON THE EFFICACY OF THE DRUG IN CHILDREN WITH TUBERCULOUS MENINGITIS OR PRIMARY TUBERCULOSIS. R. BULGARELLI and L. BUFFONI, Minerva pediat. **4**:387 (May 31) 1952.

Isoniazid (the hydrazide of isonicotinic acid) has been cautiously tested first with dogs and later with adults and children with tuberculosis in order to establish a safe dose with maximum efficiency. Especial attention has been given to the use of this drug intrathecally and to its possible injection into the cisterna cerebellomedullaris.

In dogs weighing 4 to 7 kg., 5 mg per kilogram was the maximum dose which could be given intrathecally or by cisternal puncture.

Daily doses by mouth of 8 to 10 mg. per kilogram in four divided doses was established for small children and 6 to 7 mg. per kilogram for older children with pulmonary tuberculosis.

The intrathecal use of the drug was found to lead to a serious meningitis; this was no more marked, however, than when penicillin or streptomycin was similarly used. The intrathecal dose established by tests and experience has been 1 to 1.5 mg. per kilogram for children up to 6 years of age and 1 mg. per kilogram for older children.

As to their limited clinical experience with the drug in tuberculous patients, the authors report that over a short length of time much the same results were obtained in patients with meningitis as when streptomycin was used. One adult who had a sensitivity to streptomycin reacted very favorably to this drug. In patients with pulmonary and lymph node tuberculosis, the drug was found to have a definite therapeutic value, although it was not the "miraculous" cure one might have expected from the early publicity received.

The drug will be useful in cases caused by streptomycin-resistant organisms and in cases of hypersensitivity to streptomycin. The drug is not incompatible to streptomycin; therefore, the use of these two drugs together may prove of great value.

HIGGINS, Boston.

RELATION OF THE TOTAL PROTEIN OF THE SERUM TO THE SEDIMENTATION RATE IN TUBERCULOUS MENINGITIS IN THE COURSE OF STREPTOMYCIN THERAPY. F. RAGAZZINI, Riv. clin. pediat. **48**:753 (Dec.) 1950.

The author has conducted a comparative research between the rate of sedimentation and the serum-protein grade (calculated from the specific weight with Barbour and Hamilton's method) in 20 cases of tuberculous meningitis treated with streptomycin.

From the data resulting from the 250 parallel determinations that have been taken, the author has found that, on the whole, the rate of sedimentation is proportionate to the protein substance contained in the serum.

In some cases in which the normality of the rate of sedimentation was in contrast with the seriousness of the clinical symptoms, the author has ascertained a decrease in serum proteins that might explain this exceptional and paradoxical behavior.

FROM THE AUTHOR'S SUMMARY.

THE FOURTH DIMENSION IN PROTECTION OF CHILDREN OF SCHOOL AGE. MEGIAS VELASCO, Acta pediat. españ. **10**:395-413 (June) 1952.

The author reviews the findings in mass tuberculosis studies among school children and discusses the preventorium, BCG, and other plans for control.

Not only must the teachers and the children be free of the disease but also the numerous vendors of candies and peanuts who surround the schools. An outline for the education of children in hygiene is given. The sanitary facilities of schools must be improved. The nutrition must be adequate.

More than 17,000 children were examined, and figures on the incidence of various lesions are given.

Dr. Velasco quotes Behring's famous statement: "Adult tuberculosis is merely the last stanza of a song begun in infancy." The title is derived from his thesis that there should be more cooperation among all agencies as well as among the schools and the medical profession to eliminate this disease. Physicians can no longer afford to be interested in only the individual patient and his family but should include the entire social structure of which the school child is only a part.

In this mass study, welfare, health, church, and labor organizations gave their assistance.

ALLEN, San Francisco.

SOME COMMENTS ON THE GENERAL STATE OF HEALTH AND PRODROMAL SYMPTOMS IN CHILDREN WITH HILAR PULMONARY TUBERCULOSIS. MATEO LARRAURI and LUCIANO DE LA VILLA, Acta pediat. españ. **10**:593-599 (Aug.) 1952.

This is a very colorful description of children who have hilar pulmonary tuberculosis but whose illness is undiagnosed for various reasons. To put it in the language of their parents, they have frequent intestinal upsets and many colds, feel tired, seem cross without apparent provocation, or simply "have decimas" which is equivalent to saying in English "have a temperature."

These children frequently are taken from physician to physician or are not given any medical care.

The discussion then proceeds with the diagnosis of pulmonary tuberculosis in children and with the pathology of hilar infections.

The instability of the temperature graph is just one of many liabilities, such as poor growth and development curves, alternating flush and pallor, poor appetite, and moods which are also up and down. The child unable to express any of this constantly wears the expression of one who looks for a refuge to liquidate his state of malaise.

Anxiety on the part of the parent and a disturbed household do not help. These children need plenty of rest and understanding.

ALLEN, San Francisco.

TUBERCULOMA OF BULBAR REGION. JAIME ELIAS and ALVERO COMA, Rev. españ. pediat. **7**:819-837 (Nov.-Dec.) 1951.

The authors give a detailed clinical history of a 5-year-old girl with pulmonary tuberculosis in whom there developed neurological symptoms not characteristic of meningitis but of a tumor mass or some similar lesion which would affect the nuclei of the various cranial nerves, with no marked pyramidal tract involvement. The authors describe fully the clinical course, with minute study of neurological changes, for a period of one year, when the child died suddenly.

The autopsy on the brain showed no evidence externally, but sections in series showed a very large tuberculoma on the right side, extending from the corpus callosum to the fourth ventricle. Two very small lesions were found in the left cerebellar hemisphere. The lesions had all the characteristics of a tuberculous lesion, including central caseation and some calcification.

The authors think the unmyelinated nuclei have a greater vulnerability to the tubercle bacilli than do the myelinated tracts of the central nervous system.

ALLEN, San Francisco.

A Contribution to the Significance of Infection with Bovine Tuberculosis in Allgäu. P. Mutschler, Deutsche med. Wchnschr. **77**:916 (July 18) 1952.

Allgäu is a district in southern Germany. The children of a public school, 1,424 in number, were tuberculin tested. Positive reactions were registered in 42.5%. This was correlated with the high frequency of tuberculosis among cattle (82%). X-ray examination of 567 infected children demonstrated calcified abdominal tuberculosis in 43.2%, calcified cervical lymph node tuberculosis in 3%, and tuberculous lesions of the lungs in 15.7%. These findings speak for an infection with bovine tubercle bacilli. Although the course of the abdominal tuberculosis was surprisingly benign, the author warns against a too optimistic evaluation and points again to the danger of raw milk consumption.

Amberg, Rochester, Minn.

Is It Justified to Institute Postnatal Preventive Treatment of Congenital Lues? L. Arzt and G. Gumpesberger, Wien. klin. Wchnschr. **64**:688 (Aug. 29) 1952.

Postnatal preventive treatment is given to infants of syphilitic mothers—infants who do not present clinical, x-ray, or serological manifestations of congenital syphilis, that is, those in whom a syphilitic infection cannot be definitely proved. The designation "luetic mothers" is discussed. Three groups are distinguished: (1) the group in whom a syphilitic disease could be diagnosed before delivery; (2) the group to whom prophylactic treatment was given on suspicion of a syphilitic infection without exact diagnosis; to this group belong mothers who were treated preventively as infants on account of a possible infection, and, (3) the group in whom syphilis was found after delivery but in whom clinical examination of mother and child together with the history made it likely that infection of the mother took place before delivery. The discussion of the various factors entering into consideration lead to the conclusion that, provided a sufficient prophylactic treatment of the mother has been given during pregnancy, a postnatal preventive treatment of the infant in every case cannot be demanded.

Amberg, Rochester, Minn.

Congenital Toxoplasmosis. S. Gard, J. H. Magnusson, and E. Hagberg, Acta pædiat. **41**:15 (Jan.) 1952.

After a description of the classical syndrome in congenital toxoplasmosis five cases encountered by the writers are presented. In one of these patients who was observed during the active stage of the process, Toxoplasma was demonstrated in the ventricular fluid. This case displayed all the typical signs and symptoms of the disease. The other cases displayed varying degrees of severity, and the diagnosis in these patients is based on the results of the serologic examinations. In an unequivocal case of Toxoplasma infection (asymptomatic) in the mother, a large diaphragmatic hernia was observed in the premature infant. Unfortunately, this case was not investigated satisfactorily, and it is not possible to make any statement regarding the cause of the abnormality. A follow-up investigation on six mothers of infants with diaphragmatic hernia failed to yield evidence in support of the theory that toxoplasmosis might be a cause of such malformations.

From the Author's Summary.

Clinical Sympomatology of Human Toxoplasmosis. J. Henning Magnusson, Nord. med. **45**:344 (March) 1951.

This is a short report of experiences in Sweden with toxoplasmosis. In two patients peripheral lymph node involvement was the only clinically demonstrable symptom, resembling the clinical picture of an infectious mononucleosis. One patient was infected by pricking a finger in a laboratory and presented only very mild lymphangitis and lymphadenitis. In one case the only clinically demonstrable symptom consisted of acute unilateral choroiditis.

Wallgren, Stockholm, Sweden.

Middlebrook-Dubos Agglutination Test After BCG Vaccination. Jan C. Ulstrup, Nord. med. **46**:1168 (Aug.) 1951.

Three persons that had remained tuberculin negative after BCG vaccination were again intradermally vaccinated with BCG. At the same time a tuberculin test and Middlebrook-Dubos test were made simultaneously. In all three persons a distinct antibody increase was evident

already five days after vaccination. In one of the persons it continued to increase during the following three months; in the other two the antibody titer was low at that time. The tuberculin dermally vaccinated with BCG. At the same time a tuberculin test and Middlebrook-Dubos test in the first case became positive; in the other two it remained negative.

WALLGREN, Stockholm, Sweden.

Diseases of Blood, Heart and Blood Vessels, and Spleen

ACUTE BENIGN PERICARDITIS IN CHILDHOOD: COMPARISONS WITH RHEUMATIC PERICARDITIS, AND THERAPEUTIC EFFECTS OF ACTH AND CORTISONE. SIDNEY FRIEDMAN, RACHEL ASH, T. N. HARRIS, and HENRY F. LEE, Pediatrics **9**:551 (May) 1952.

Six cases of acute benign pericarditis in childhood have been studied. The importance in childhood of the differentiation of acute benign pericarditis from acute rheumatic pericarditis has been emphasized and demonstrated by a comparison of the clinical findings and subsequent courses in patients with these two types of pericardial involvement. The results of treatment of acute primary pericarditis with the hormones corticotropin (ACTH) and cortisone are presented and discussed. Some negative findings in the study of the etiology of this disease are presented.

FROM THE AUTHORS' SUMMARY.

IDIOPATHIC HYPOPROTEINEMIA: REPORT OF A CASE OF TRANSIENT EDEMA, DEPRESSION OF PLASMA ALBUMIN AND GAMMA GLOBULIN AND EOSINOPHILIA. JAMES B. WYNGAARDEN, JOHN D. CRAFORD, HARRIE R. CHAMBERLIN, and WALTER F. LEVER, Pediatrics **9**:729 (June) 1952.

A 3½-year-old Negro boy with an obscure syndrome of inexplicable, transient, acquired hypoproteinemia, involving plasma albumin and especially gamma globulin, has been observed. Edema, oliguria, and weight gain were noted 10 days after an attack of acute tonsillitis. Hypertension, renal impairment, proteinuria, and hematuria were conspicuously absent, and an associated eosinophilia subsided as recovery progressed. Plasma protein regeneration was complete in 10 weeks. Since then mild asthma has developed, but the patient has otherwise remained well.

This appears to be an unusual case of transient derangement of plasma protein metabolism. Possible relationships to the syndromes of acute nephritis without proteinuria, nephrosis, serum sickness, and idiopathic acquired hypoproteinemia are discussed.

FROM THE AUTHORS' SUMMARY.

AMINO ACID METABOLISM IN PATIENTS WITH ACUTE LEUKEMIA. HARRY A. WEISMAN, ROBERT A. PASTEL, and HENRY O. PONCHER, Pediatrics **10**:653 (Dec.) 1952.

The free phenylalanine and tyrosine levels in the plasma of patients with acute leukemia are significantly higher than in normal patients. Tyrosine and tyrosine metabolites in the urine are apparently normal, in spite of the higher blood amino acid levels. The hyperpigmentation that has been observed in patients receiving folic acid antagonists cannot be directly related to tyrosine excretion in the urine or to the elevated melanin precursors in the blood, but is probably due to interference with the normal inhibitors of melanogenesis in white skin by the antagonists. Additional proof for this speculation is necessary. Isoleucine was higher in the plasma of leukemic patients, and creatine values in urines of leukemic patients were within normal range.

FROM THE AUTHORS' SUMMARY.

EXCHANGE TRANSFUSION AND TRANSFUSION IN INFANTS AND YOUNG CHILDREN. J. A. DIQUE, M. J. Australia **1**:764 (May 30) 1953.

The author has devised a method of working out the percentage of the baby's blood exchanged in which various amounts of blood are used in each injection. He finds that there is no significant difference when 1 cc. amounts are used as compared with 20 cc. amounts, but feels that 15 to 20 cc. amounts are preferable because of the smaller time required. When twice the baby's blood volume is transferred, the average percentage of exchange is about 87%. Dique suggests as a rough estimate of the amount of blood needed for 90% replacement 100 cc. more than 100 times the baby's weight in pounds—e. g., 700 cc. for a 6-lb. baby.

MCGUIGAN, Evanston, Ill.

So-Called Tropical Eosinophilia. Shantilal C. Sheth, Indian J. Pediat. **20**:106 (May) 1953.

Sheth reviews the symptomatology, physical signs, radiological findings, and course, as well as treatment, in 32 cases of tropical eosinophilia. Various theories regarding etiology are discussed. The author suggests a new name, systemic eosinophilosis.

McGuigan, Evanston, Ill.

Management of Heart-Failure in Infants and Children of Non-Rheumatic Origin. L. S. N. Prasad, Indian J. Pediat. **20**:113 (May) 1953.

Prasad states that treatment of nonrheumatic cardiac failure depends on the underlying etiology. The author cites such causes as diphtheria, typhoid, pneumonia, toxic polyneuritis, acute nephritis, and beriberi. Brief mention of treatments is given.

McGuigan, Evanston, Ill.

Influence of Exsanguination Transfusion on the White Blood Corpuscles. H. Kolbl, Ann. pædiat. **179**:100 (Aug.) 1952.

During exsanguination transfusion the blood proteins of the child assume the values of the donor blood. In the nephrotic syndrome the lipoproteids decrease rapidly, while the γ-globulins increase. In hemolytic disease there exists a hypoproteinemia with a relative hypalbuminemia, a fact which explains the proneness to edema and shock. Rh-negative blood donors frequently exhibit a protein deficiency on account of their giving blood frequently at short intervals. The blocking antibodies disappear during the exchange transfusion after about 150 cc. has been given. Therefore there is no reason to be afraid of an increase of the avidity of the blocking antibodies caused by a higher concentration of the albumins in the donor blood.

From the Author's Summary.

Normal Values for Reticulocytes in Childhood. Elsa de Chastonay, Helvet. paediat. acta **6**:257 (June) 1951.

The reticulocyte count of normal children aged 1 to 10 years was determined during 10 days. There were 10 cases for each year group. The author used the technique of Wolfer, with brilliant cresyl blue, and counted on the basis of 5,000 erythrocytes (dry preparation) with reflected light.

The normal count of reticulocytes remains unchanged from the first to the tenth year. The values vary from 3 to 20%, mainly from 4 to 12%. Variations below the minimum value are rare, while those above the maximum value are oftener to be met with. Values less than 3% are suspect of abnormal maturation processes in the bone marrow (reticulocytopenia). Values above 20% are not so very rare but may be interpreted as a sign of some disturbance in erythropoiesis. In the same case, the reticulocyte values do not show any daily variation. The differentiation of the reticulocytes, using the method of Heilmeyer, has shown that Type II is seldom, and Types III and IV are chiefly, represented. We found a slight preponderance of Group IV. Routine determination of reticulocytes in cases of the Kinderspital chosen at random produced almost the same results as in the cases cited above.

Grulee, Evanston, Ill.

Essential Chronic Granulocytopenia in Childhood. C. Gasser and M. R. Vrtilek, Schweiz. med. Wchnschr. **82**:1122 (Oct. 25) 1952.

Under exclusion of granulocytopenia of known origin, the essential chronic form demands that the number of neutrophile elements in the blood drop below 1,000 for a period of at least three months. Four girls and two boys were observed on being admitted to the hospital at ages of 15 days to 31 months. The changes in the peripheral blood as well as those of the bone marrow are discussed briefly. The disease has proved resistant to therapy; it may extend over months and years, usually with spontaneous healing. The differential diagnosis is discussed. With regard to pathogenesis and etiology, allergic factors are accepted as certain. More detailed presentations are given or are to be given elsewhere.

Amberg, Rochester, Minn.

IDIOPATHIC CARDIAC HYPERTROPHY. D. P. R. KEIZER, Riv. clin. pediat. **50**:470 (July) 1952.

The author has studied three cases of so-called "idiopathic heart hypertrophy." The first case was caused by acute interstitial myocarditis Type Fiedler; the second, by cardiomegalia glycogenica, and the third, by the anomalous origin of the arteria coronaria cordis.

FROM THE AUTHOR'S SUMMARY.

MEASURING OF THE BLOOD PRESSURE IN INFANTS. E. HOEN, Ztschr. Kinderh. **70**:441 (May) 1952.

The author used a mechanism consisting of two small chambers fixed on two metal arms, between which the ear lobe of the child is placed. The lower chamber is covered with a convex glass plate and contains a small light bulb; the upper chamber has on one end a thin rubber membrane which is fitted on the ear lobe and a lens on the other end and is equipped with a rubber tube, through which air is pumped into it. By the increased pressure the membrane is made to bulge and compress the ear lobe. The air pressure is slowly released, and with the appearance of the visible pulsation of an artery in the ear lobe the systolic pressure is read on a mercury sphygmomanometer. On further release the visible pulsations stop, and this constitutes the diastolic pressure.

The author feels that the method for the diastolic pressure determination must still be improved. He attributes the great variations in the systolic pressure which he found to actual instability of the blood pressure of the infant.

GLASER, Jerusalem, Israel.

MICROSCOPY OF BLOOD CELLS. W. KOSENOW and H. MAI, Ztschr. Kinderh. **70**:552 (June) 1952.

Various fluorochromic substances were tested on dried blood slides but did not offer more information than regular stains. Supravital stains, however, with acridine orange added seem to give results which are influenced by the functional state of the cell and may thus give additional information.

GLASER, Jerusalem, Israel.

SYSTOLIC AND DIASTOLIC TIME AS A FUNCTIONAL TEST OF THE HEART IN CHILDREN. G. W. JACOBI and H. KIRCHHOFF, Ztschr. Kinderh. **70**:561 (June) 1952.

The authors define the time of muscle tightening (*Anspannungszeit*) as the time measured from the beginning of the Q wave in the electrocardiogram to the onset of the amplitude of the carotid pulse curve, minus the delay caused by the recording apparatus of the carotid pulse curve (zero for the electrocardiogram) and the delay of the pulse wave from heart to carotid. The expulsion time (*Austreibungszeit*) was measured from the onset of the carotid pulse to the depth of the notch.

In a study of normal and cardiac children the authors determined normal values for children and found a prolongation of the *Anspannungszeit* in cardiac failure and myocardial damage; the *Austreibungszeit*, however, appeared to be dependent upon the ventricular volume.

GLASER, Jerusalem, Israel.

CIRCULATORY MEASUREMENTS AND REGULATIONS IN CHILDHOOD. H. KIRCHHOFF and G. W. JACOBI, Ztschr. Kinderh. **70**:578, (June) 1952.

Normal values for various ages for ventricular output, minute output, elastic and total resistance of the arterial system, and cardiac labor and efficiency were determined and compared with values found for children during puberty, children who showed signs of precocious development, patients with endomyocarditis, and patients with congenital heart disease.

GLASER, Jerusalem, Israel.

Diseases of Nose, Throat, and Ear

Nasopharyngeal Radium Treatment. Walter E. Loch and Newton D. Fischer, Ann. Otol. Rhin. & Laryng. **61**:198 (March) 1952.

Loch and Fischer examined 85 patients who had received nasopharyngeal radium treatment from 3 to 29 years previously. No late detrimental effects of the irradiation or any visible tissue changes due to radium application were found.

The Eustachian tubal orifices were not overgrown by lymphoid tissue in any of the patients; this would indicate the effectiveness of the nasopharyngeal radium applicator in the hands of Crowe and his associates.

Hearing was usually improved over the preirradiation level provided the impairment was not due to otosclerosis, perceptive loss of hearing, or chronic adhesive middle-ear disease that interfered with the movements of the ossicular chain.

It is explained that radium is used not for the purpose of restoring the basic hearing defect in such cases but to provide prophylactic benefits against further loss of hearing due to colds, acute and chronic nasal pharyngitis, and interference with tubal function.

Steele, Kansas City, Kan. [A. M. A. Arch Otolaryng.].

A Prolonged Local Anesthetic in Control of Post-Tonsillectomy Pain. Morris Davidson, Robert G. Boles, and Sanford C. Snyderman, Ann. Otol. Rhin. & Laryng. **61**:1046 (Dec.) 1952.

Interested in earlier favorable reports on the use of a solution of procaine hydrochloride and butyl aminobenzoate in a stable water-miscible, nonoily vehicle (Efocaine) for the control of pain following tonsillectomy, the authors treated 27 patients undergoing tonsillectomy by mucosal injection of the solution along both anterior and posterior pillars.

Davidson and his associates conclude that the agent is of questionable value in reducing pain after tonsillectomy.

Steele, Kansas City, Kan. [A. M. A. Arch Otolaryng.].

Use of a Group Structure in Speech Therapy. Ollie Backus, J. Speech & Hearing Disorders **17**:116 (June) 1952.

Language and disordered language as behavior can be best varied in a group situation, since each client must do his own changing. The group provides an atmosphere in which a client can feel acceptance, facilitates observation of the client, and provides better availability of tools with which a client can move ahead. Critical changes in behavior are viewed as those occurring at dynamic levels.

Palmer, Wichita, Kan.

Differentiation of Interiorized and Exteriorized Secondary Stuttering. Ernest Douglass and Bruce Quarrington, J. Speech & Hearing Disorders **17**:377 (Dec.) 1952.

Stutterers can be divided into two types: those who attempt to mask their stuttering, and those who attempt to avoid it by devices. The interiorized stutterer wants to avoid stuttering. The exteriorized stutterer wants to express himself. Interiorized stutterers appear to come from families that are upwardly oriented and employ child-rearing practices and methods of discipline particularly suited to children who are to maintain the social status of the family. Case histories show that the families of interiorized stutterers showed earlier and greater concern for speech behavior.

Palmer, Wichita, Kan.

A Medicine Bag for the Speech Correctionist. Dorothy Bell and E. L. Pross, J. Speech & Hearing Disorders **17**:397 (Dec.) 1952.

The authors describe the minimum tools needed by the speech correctionist.

Palmer, Wichita, Kan.

VOCAL RESPONSES DURING CONTROLLED AURAL STIMULATION. CHESTER J. ATKINSON, J. Speech & Hearing Disorders **17**:419 (Dec.) 1952.

Twenty-four men read 90 monosyllables during successive exposures to tones of varying loudness and frequency given three seconds before the speaker reads each syllable. The sound pressure level of vocal responses tended to increase as the loudness level was increased. The frequency of the stimulus did not affect the sound pressure level. The loudness level of the stimulus raised the response frequency. The frequency of the stimulus tone had no effect on the fundamental frequency in the voice. Speakers change their voices in response to differences in the acoustic environment relative to loudness of the stimulus tones in that environment.

PALMER, Wichita, Kan.

THE COMMON HAZARDS OF GENERAL ANESTHESIA FOR TONSILLECTOMY AND ADENOIDECTOMY. KENNETH F. EATHER, Northwest Med. **51**:671 (Aug.) 1952.

There is little doubt that the major hazard of tonsillectomy and adenoidectomy is the anesthetic. Only in the case of overwhelming or neglected hemorrhage does the patient die of surgery per se. Most deaths occurring during or immediately after a tonsillectomy are due to anoxia, anesthetic overdosage, or hemorrhage. The complications other than hemorrhage can be materially decreased by the more widespread and intelligent use of endotracheal technique by the physicians. This technique minimizes the pharyngeal or laryngeal obstruction, laryngeal spasm, and aspiration which are antecedent to the more serious complications.

Psychologic trauma is a related hazard of anesthesia, and this problem must be approached by the parents, hospital attendants, and physicians in a manner which will minimize the patient's fears and apprehensions over an unknown and terrifying experience. This is an all-too-neglected phase of pediatric surgery which must be corrected.

DOCTER, Seattle.

COMPARATIVE EFFECTS OF PENICILLIN, AUREOMYCIN, AND TERRAMYCIN ON STREPTOCOCCAL TONSILLITIS AND PHARYNGITIS. FLOYD W. DENNY, LEWIS W. WANNAMAKER, and EDWARD O. HAHN, Pediatrics **11**:7 (Jan.) 1953.

The effects of penicillin, chlortetracycline (Aureomycin), and oxytetracycline (Terramycin) on the clinical course of streptococcal tonsillitis and pharyngitis were compared in a controlled study. Under therapy with these agents, most of the symptoms and signs subsided somewhat more rapidly than in control patients, leucocytosis was reduced, and antibody formation was diminished, but in the dosage used no one drug was consistently more beneficial than the others. Penicillin was the most effective drug in eradicating streptococci from the throat. Nausea and vomiting occurred frequently among patients receiving chlortetracycline and diarrhea was common in both the chlortetracycline and the oxytetracycline treated groups. Final determinations of the drug of choice should await comparison of the effects on suppurative and nonsuppurative complications in larger groups of patients.

FROM THE AUTHORS' SUMMARY.

THE INTELLIGENCE OF CHILDREN WITH ADENOIDS AS SHOWN BY THE TERMAN-MERRILL TYPE L TEST OF 1937. G. MORA, Minerva pediat. **4**:482 (June 30) 1952.

Intelligence tests were made on 30 children with obstructive adenoid tissue and 30 control children in a grade school in Genoa. Not all children with adenoids were retarded mentally. Adenoids which had led to stunted physical growth also led to a lower intellectual attainment. Heredity was definitely a larger factor than adenoids in affecting intellectual achievement. The scholastic achievements of the children with adenoids paralleled the intelligence quotients.

HIGGINS, Boston.

REPORT OF FIFTEEN CASES OF AGENESIS OF THE EXTERNAL AUDITORY CANAL. J. M. TATO, J. A. BELLO, and J. L. CASTELLANO, Acta oto-rino-laring. ibero-am. **4**:85, 1953.

Tato and his associates discuss both unilateral and bilateral agenesis of the external canal. They believe that an operation should be performed in cases of bilateral agenesis when the patient is 3 or 4 years old, so that the benefits of hearing may be associated with the development of the

intellect, language, and education. Early treatment is most important. In cases of unilateral agenesis the physician may temporize. In cases of bilateral agenesis it is important to operate in order to (*a*) favor stereoacusia; (*b*) prevent deafness; (*c*) avoid possible intracranial complications; (*d*) solve the esthetic and psychologic problems of the patient, and (*e*) prepare a useful cavity should a hearing aid be necessary in later life. The surgical technique is divided into three portions: (*a*) a bony procedure, namely, a complete mastoidectomy; (*b*) fenestration, and (*c*) the insertion of a skin graft in the form of a finger of a glove. The results in 15 cases are reported, revealing a marked improvement in hearing in a majority of the patients.

PERSKY, Philadelphia [A. M. A. ARCH. OTOLARYNG.].

TUBERCULOUS OTITIS MEDIA. LENNART GISSELSSON, Nord. med. **47**:366 (March) 1952.

The author reports a case of a 12-year-old girl who recovered from tuberculous otitis media. The diagnosis was overlooked for a long time. Characteristic features were the swelling of the preauricular and postauricular lymph nodes. Medication with *p*-aminosalicyclic acid and streptomycin will probably produce a cure and thereby render surgical intervention unnecessary.

WALLGREN, Stockholm, Sweden.

Diseases of Lungs, Pleura, and Mediastinum

THE POSTNATAL STRUCTURAL CHANGES IN THE INTRAPULMONARY ARTERIES AND ARTERIOLES. W. HAROLD CIVIN AND JESSE E. EDWARDS, A. M. A. Arch. Path. **51**:192 (Feb.) 1951.

The intrapulmonary arteries and arterioles of the fully developed lungs go through stages which can be traced microscopically from fetal life until the time that adult size and appearance are reached. In the fetus and at birth the elastic arteries are open, but the ratio of the thickness of the wall to the diameter of the lumen is high and the adventitia is thick. With growth, the circumference of the wall becomes greater; more elastic fibers are deposited in the media; the ratio of the thickness of the wall to the diameter of the lumen becomes lower, and the adventitia becomes thinner. The lumen of the muscular artery is narrow before birth. Growth of these vessels follows the same course as that of the elastic vessels. The arterial vessels of the lung show adult characteristics at the age of 6 months. Before that time arterioles become recognizeable. These gradually show wider lumens, and the walls always remain thin. By the age of 21 years elastic tissue is found in the walls of the arterioles. Full growth of vessels appears to be achieved at about the age of 21 years.

HAW CHAN, San Francisco.

Diseases of Gastrointestinal Tract, Liver, and Peritoneum

MUCOEPIDERMOID CARCINOMA OF THE PAROTID GLAND IN AN EIGHT-YEAR-OLD GIRL. HORACIO ZALCE, ALEJANDRO AGUIRRE, MAXIMILIANO SALAS, ERNESTO CONTRERAS, LUIS VARGAS Y VARGAS, and CARLOS SARINANA, Bol. méd. Hosp. inf. **10**:166 (April) 1953.

The authors present a case of mucoepidermoid tumor of the right parotid gland in an 8-year-old girl. This type of neoplasm is very rarely seen in children. In the American medical literature up to 1951, only five such cases are mentioned. The case under consideration is the first reported in the Mexican medical literature.

This tumor progressed rather slowly for a little over a year, giving place to a large cyst which formed fistulas in two places. Contrary to expectations, considering the ideas of Stewart and co-workers, this cystic tumor behaved as though highly malignant after partial excision, since before a month's time caused a large node in the sternocleidomastoid muscle and metastases to the lateral chain of lymph nodes of the neck. The behavior of the neoplasm made necessary a total parotidectomy with radical dissection of the neck.

Since there is hardly any experience in this type of tumors in children, for the time being no prognosis can be ventured.

FROM THE AUTHORS' SUMMARY.

MECONIUM ILEUS WITHOUT CYSTIC FIBROSIS OF THE PANCREAS. SEIGFRIED SPÖRLEIN, Arch. Kinderh. **144**:63, 1952.

The author discusses a postmortem study of a 3-day-old boy who died from meconium ileus, perforation, and peritonitis. Histology neither revealed a congenital malformation nor hepatic or pancreatic alterations. Since similar cases have been recorded in the literature, the author assumes that anomalous intestinal secretions without evident anatomical abnormalities may account for this clinical picture in a number of cases. GOTTSTEIN, Chicago.

ORAL TERATOMA: OPERATION PERFORMED IMMEDIATELY AFTER BIRTH. ALF SJÖVALL, Nord. med. **46**:1531 (Oct. 10) 1951.

A giant epidermoid teratoma in a newborn child was successfully removed. At the follow-up study five years later the condition was satisfactory. WALLGREN, Stockholm, Sweden.

Nervous Diseases

ASSOCIATED MOVEMENTS BETWEEN LIMB AND RESPIRATORY MUSCLES AS A SEQUEL TO BRACHIAL PLEXUS BIRTH INJURY. P. K. ROBINSON, Bull. Johns Hopkins Hosp. **89**:21 (July) 1951.

Simultaneous contraction of muscles which do not normally act together, although supplied by the same nerve, has long been observed to follow injury of that nerve. In an effort to observe the frequency of this associated activity, all adults whose records were available through the files of a general hospital and who had had damage to the brachial plexus at birth were examined for evidence of such movements. The results in a series of eight unselected persons, examined at intervals of from 9 to 23 years after injury, are the subject of this report.

Associated movements of muscles of respiration and of partially paralyzed limb muscles, as shown by contraction of the latter during deep inspiration, were found in six of the patients. To demonstrate that such abnormal activity might occur as a result of damage either to the phrenic nerve or to the nerve supply to the accessory respiratory muscles, the author studied the effect of use of the limb muscles on those of respiration. Fluoroscopic study of five of the six patients demonstrated diaphragmatic contractions in three when the elbow was flexed. In one patient contraction of the limb muscles produced associated activity in one of the superficially placed accessory respiratory muscles.

According to Robinson, an explanation of the abnormal simultaneous activity of the limb and the respiratory muscles is possible on a structural basis. The respiratory muscles in question are the diaphragm and the accessory muscles of respiration, namely, the trapezius, sternocleidomastoid, pectoralis, latissimus dorsi, and scalenus muscles. All the accessory group except the first two are supplied by nerves having their origin in the fifth to eighth cervical and first thoracic roots, which form the brachial plexus and supply the limb muscles also. The part of the diaphragm which arises from the septum transversum is innervated by the phrenic nerve, which itself receives a rootlet from the fifth cervical root. Injury to the fifth root proximal to the origin of this rootlet may permit the central regenerating fibers, which originally went to the arm, to descend into the phrenic nerve and innervate the diaphragm; thereby contraction of the limb muscles will cause the diaphragm to descend. Similarly, contraction of accessory respiratory muscles may occur during limb movements when the plexus itself is damaged at a point where innervating fibers run close together. The converse, namely, contraction of arm muscles during inspiration, may be produced by injury at either of the sites mentioned. Robinson believes that this phenomenon is much more frequent than has hitherto been thought.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

SURGICAL TREATMENT OF INFANTILE HYDROCEPHALUS. TRACY J. PUTNAM, California Med. **78**:29 (Jan.) 1953.

The operation of endoscopic coagulation of the choroid plexuses for the relief of infantile hydrocephalus is now 18 years old. Nearly 100 cases have been reported, and the indications and procedure are well standardized. Several patients have apparently grown up normally after the earliest series of operations.

In a recent series of 20 operations performed on 10 patients in the past 10 years, there have been no deaths attributable to the procedure. The operation has substantially decreased the pressure in all cases and has brought it within normal limits in all patients on whom the operation was performed before the head became grossly enlarged.

The mentality has improved following relief of pressure in all cases.

When the operation was performed before deterioration began, the results were uniformly excellent.

PRYOR, Redwood City, Calif.

ORTHOPEDIC SURGERY IN CEREBRAL PALSY. HARRY E. BARNETT, J. A. M. A. **150**:1396 (Dec. 6) 1952.

In children no surgery should be performed unless physical therapy and bracing have been unsuccessful. Some indications and contraindications for surgery are given. Nerve crushing procedures and procaine nerve blocks would seem to be worth-while trial procedures before neurectomies in some instances, but physical therapy still remains all important.

KIMBALL, Evanston, Ill.

MIGRAINE IN CHILDREN. MORRIS I. MICHAEL and JONATHAN M. WILLIAMS, J. Pediat. **41**:18 (July) 1952.

Aretaeus wrote about migraine in the first century A.D. Since then the volume of literature on this subject has been limited by only the available supply of paper.

Migraine, sometimes inherited, often affects children. Attacks are more frequent in children than in adults. Symptoms may be associated with emotional disturbances and/or with allergies and with epilepsy.

Prophylaxis consist of antihistamines, such as diphenhydramine (Benadryl), phenindamine (Thephorin), or tripelennamine (Pyribenzamine), or of combinations of ergotamine and caffeine and in convulsive patients of diphenylhydantoin (Dilantin).

MACDONALD, Pittsburgh.

SPONTANEOUS FRACTURE OF THE FEMUR IN AN INFANT WITH A LARGE OCCIPITAL MENINGOCELE. A. JUNGMANN, Radiology **61**:231 (July) 1953.

An account is given of an infant with a large occipital meningocele who acquired a fracture of the femur for which no cause could be established. The author believes that an analogy exists between the case of his patient and eight previously recorded cases of multiple fractures in patients who suffered from chronic subdural hematoma. It is suggested that the assumption of an unknown injury is not a satisfactory explanation in such cases.

ANSPACH, Riverside, Ill.

MENINGITIS IN INFANCY AND CHILDHOOD OTHER THAN TUBERCULAR MENINGITIS (AN ANALYSIS OF NINETY-EIGHT CONSECUTIVE CASES IN MADRAS DURING 1950-51). S. T. ACHAR and G. RAMA RAO, Indian J. Pediat. **20**:55 (March) 1953.

Achar and Rao analyze 98 cases of nontubercular pyogenic meningitis encountered over a period of two years. There were 45 cases of Hemophilus influenzae meningitis, 38 of pneumococcal, 12 of meningococcal, 2 of streptococcal, and 1 of Friedländer's bacillus meningitis. H. influenzae infection was overwhelmingly the most common in infancy, pneumococcal was next most common, and meningococcal third. There was no meningitis in the group of children from 2 to 5 years old.

Treatment is outlined as used. The most useful drug in H. influenzae infection was streptomycin in doses of 20 mg. per pound (0.5 kg.) of body weight per day for 7 to 10 days. Chloramphenicol (Chloromycetin) was used in only two cases because of its cost. Pneumococcal infections responded best to large parenteral doses of penicillin. Meningococcal meningitis patients received mainly sulfadiazine, and sulfadiazine and penicillin together were used in streptococcal infections.

MCGUIGAN, Evanston, Ill.

BILATERAL NASOETHMOIDAL ENCEPHALOCELE. A. MARSCHAK and G. RIESENFELD, Harefuah **45**:224 (May 15) 1953.

Marschak and Riesenfeld report a case of nasoethmoidal encephalocele in a Yemenite infant. Of 106 cases in the literature, there were only 2 in which the encephalocele was bilateral. An 8-day-old Yemenite infant had bilateral swelling of the face between the nose and the eye; the swellings were tense and bluish-red and failed to transilluminate properly. A roentgenogram of the skull showed a defect in the bone between the frontal and the nasal bones on the left; the sutures of the skull were not widened. No abnormality of the child's general condition was found, and no other defects were noted. Some of the swelling from each side of the naso-ocular region was removed, without complete disappearance of the deformities. Four weeks after the operation, at the age of 24 days, the child died. Autopsy revealed that the lamina cribrosa was absent bilaterally, and the right frontal lobe extended toward the left side through a defect in the falx membrane. The authors suggest an intracranial approach in cases of this type in the future.

N. SAVITSKY, New York [A. M. A. Arch. Neurol. Psychiat.].

ACUTE ENCEPHALITIS CAUSED BY LEPTOSPIRA HYOS FOLLOWING TRAUMATIC INFECTION. O. GSELL and A. PRADER, Helvet. paediat. acta **8**:318 (Aug.) 1953.

A case of encephalitis caused by Leptospira hyos in a 3-year-old boy is reported. The encephalitis was followed by cerebral hemiatrophy with spastic hemiparesis.

The case is of special interest because (1) it is of one of the youngest patients known with leptospirosis, (2) leptospirosis with encephalitis and permanent cerebral damage is extremely rare, (3) the infection was caused by trauma (fall into a pit of liquid hog manure).

In 96 cases of leptospirosis hyos (leptospirosis mitis Johnson) the incidence of encephalitis or myelitis was 7.3%.

FROM THE AUTHORS' SUMMARY.

RECKLINGHAUSEN'S DISEASE IN CHILDREN. M. CRISALLI, Minerva pediat. **5**:1118 (Feb. 28) 1953.

Three cases of Recklinghausen's disease in children are reported. In each case there was a localization of neurofibromata in the eye and orbit, with intracranial extension. Only 17 cases with similar involvement have been reported in the medical literature.

HIGGINS, Boston.

TREATMENT OF PNEUMOCOCCUS MENINGITIS IN INFANTS AND CHILDREN. UWE KARSTEN PETERSEN, Deutsche med. Wchnschr. **77**:1346 (Oct., 31) 1952.

Diplococcus pneumoniae meningitis was treated with penicillin intramuscularly and a sulfonamide and chlortetracycline (Aureomycin) by mouth. Of 16 patients, 1 died. Thirteen patients, including the one who died, were infants. The early mortality was lowered; the cure was more certain and more rapid, and recurrence was avoided.

AMBERG, Rochester, Minn.

TREATMENT OF FLACCID PARESIS AND ATONY OF MUSCLES IN CHILDHOOD WITH VITAMIN B_6 (PYRIDOXINE). WALTER KIRCHER, Med. Klin. **47**:1026 (Aug. 1) 1952.

Kircher reports that in some diseases of children associated with atony of muscles or flaccid paresis the administration of pyridoxine appeared to be beneficial. It seemed to aid in the restoration of function in cases of poliomyelitic paralysis. A case of progressive muscular dystrophy and two cases of congenital myotonia did not respond. Special attention is called to the euphoria produced by the treatment.

AMBERG, Rochester, Minn.

Psychology and Psychiatry

CLINICAL MANIFESTATIONS OF AUTISM AND SCHIZOPHRENIA IN CHILDHOOD. DANIEL CAPPON, Canad. M. A. J. **69**:44 (July) 1953.

Cappon points out the similarity between the manifestations of childhood schizophrenic reactions and those of mental deficiency. He notes that such schizophrenic reactions occur more frequently than is realized and believes that with psychotherapy and environmental manipulation as high as 20% of patients may be improved.

MCGUIGAN, Evanston, Ill.

TEST OF "SUDDEN RISING" AND THE PSYCHONEUROMUSCULAR BEHAVIOR IN CHILDREN. GEORGE MOURIQUAND, Presse méd. **69**:1471 (Nov. 1) 1952.

The test is derived from the routine maneuver prescribed for the myophathic patient to practice for the purpose of assessing the various phases he passes through from the recumbent position to the standing position in order to discover the degree of his neuromuscular dystrophy. The author for many years has been utilizing a similar test, excluding cases of confirmed neuromuscular changes, in order to discover how the muscular system of children as a whole responds to the sudden "command" of the nervous system. For practical purposes, the children can be grouped in three categories. The rapid type who start up like a spring. These children are nervous, hyperactive subjects. They are quick-witted, play wholeheartedly and vigorously, often extending this attitude to their school behavior. A middle type showing as less quick in the test is encountered in subjects generally quieter with a tendency towards physical and psychic asthenia especially in the hypergrowth period (prepuberty). The third category encompasses "lymphatic" subjects, lazy both intellectually and psychically. These children often show a lowered basal metabolism and occasionally an elevated vestibular chronaxia.

The last group should particularly interest the physician and teacher, for they may improve (increase in the rapidity of the test and in the school behavior) with the use of associated opotherapy-vitaminotherapy supplementary muscular training. The test may also provide information on the improvement of convalescents and have bearing on the "psychoneuromuscular command" of certain choreatic, poliomyelitic, mongolian, and myxedematous subjects under treatment.

FROM THE AUTHOR'S SUMMARY.

HELLER-ZAPPERT DISEASE (INFANTILE DEMENTIA). D. L. OUTES and A. M. FIERRI, Prensa méd. argent. **40**:458 (Feb. 20) 1953.

Heller, in 1908, and Zappert, in 1921, described a form of dementia in children. The affected children develop normally up to the third or fourth year, when language disorders appear, which are soon followed by mental changes, restlessness, and progressively severe dementia. The children do not usually look like imbeciles or idiots. No neurologic signs were reported. The facial expression remains fairly normal in spite of the deterioration. In 1926, Corberi reported the first anatomic studies in two cases of this type; in both anatomic changes of amaurotic familial idiocy were apparent. Weygandt, in 1933, reported a case in which degenerative changes were present in ganglion cells of the brain; the degenerative changes noted by Corberi were not found.

The authors report the first case of Heller-Zappert disease (infantile dementia) in Argentina. The boy developed normally until his fourth year. Two months after he was frightened by a barking dog he began to have language difficulties. His speech became progressively worse, and he became very restless and had difficulty in taking care of himself. Some ability to appreciate and to react emotionally to music was conserved. Psychiatric studies, at the age of 12 years, showed utter inability to speak, evident dementia, restlessness, and incoordinated movements of the upper extremities. The affective reactions were defective. The neurologic findings were entirely normal. Spinal fluid studies showed a total protein content of 29 mg. per 100 cells, 3 cells per cubic millimeter, and a negative Wassermann reaction. Pneumoencephalography showed a dilated ventricular system and cortical atrophy.

N. SAVITSKY, New York [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

Diseases of Genitourinary Tract

TREATMENT OF NEUROGENIC URINARY AND FECAL INCONTINENCE IN CHILDREN. R. E. GROSS; G. W. HOLCOMB JR., AND H. SWAN, A. M. A. Arch. Surg. **66**:143, 1953.

In children, the treatment neurogenic disturbances of the bladder and rectum presents perplexing problems. Urinary and fecal incontinence usually are the result of lumbosacral myelodysplasia, meningomyelocele, or lipoma. Children with these lesions are constantly uncomfortable, wet, and smelly, being soiled by their excretions. Since the skin around the genitalia, perineum, and thighs is apt to become macerated and infected, the nursing problem is most difficult. The authors report their experiences with 21 such cases. Local corrective

procedures should be tried only after all means of neurosurgical repair have been exhausted. Below an age of 4 years, mild urinary incontinence may not require surgical treatment but may respond to bladder training. In the "overflow bladder," with excessive sphincter tone, transurethral resection of the bladder neck may be beneficial; occasionally, however, this operation makes the situation worse by causing constant dribbling.

Surgical repair of relaxed anal and rectal sphincters should not be attempted before an age of 5 or 6 years. If only rectal incontinence is present, the combined use of constipating diet and daily cleansing enemas may prove satisfactory; at any rate, colostomy will be of no benefit. In some instances, surgical reduction of the bladder outlet by plication of the bladder wall will successfully overcome the constant dribbling. If the patient has severe incontinence, a so-called wet colostomy is indicated (it discharges both fecal material and urine). The excretions are collected in a colostomy bag, which has to be cemented to the abdominal wall and contains a disposable plastic sac. It is inadvisable to construct a new bladder from the sigmoid. Diversion of the urine from the perineum can be accomplished by interruption of the urethra, closure of the bladder outlet, and establishment of a permanent suprapubic cystotomy. The cystotomy tube may be clamped, provided the urethrovesical valves are competent and renal function is adequate; otherwise, the tube should be left open.

Constant medical supervision of these children is mandatory to prevent complications.

List, Grand Rapids, Mich. [A. M. A. Arch. Neurol. & Psychiat.]

Diseases of Ductless Glands; Endocrinology

Decrease in the Formation of Adrenocorticotropin Following Administration of Epinephrine. Carl A. Gemzell, Endocrinology **50**:399 (April) 1952.

It has been suggested that one of the mechanisms controlling the release of corticotropin (ACTH) from the pituitary is activation of the sympathetic nervous system. Through the release of epinephrine from the adrenal medulla, the anterior pituitary is activated. Epinephrine is then thought to act directly on the pituitary cells. But others bring evidence that epinephrine has no direct effect on pituitary activation of ACTH but acts like other nonspecific stresses by changing the levels of cortical steroids in the circulation.

In this paper it is shown that in adrenalectomized rats, epinephrine causes the level of corticotropin in the body fluids to drop, through a direct inhibitory effect on the formation of corticotropin in the pituitary. In normal rats epinephrine causes the level of corticotropin in the body fluids to increase through an indirect stimulatory effect on the corticotropin secretion from the pituitary.

Jacobsen, Buffalo.

The Relationship of Corticoid Excretion to Ovarian Hormones in the Guinea Pig. Bernard Zondek and Shlomo Burstein, Endocrinology **50**:419 (April) 1952.

It is shown that the guinea pig under certain conditions is a very sensitive and suitable animal for the study of adrenocortical function by the chemical determination of urinary corticoids. By this method it is demonstrated that (1) adrenocortical function is cyclical and increased at the time of estrus, (2) adrenocortical activity is low and acyclical in the absence of the ovary and in the male guinea pig, and (3) adrenocortical activity is increased by the administration of estrogens.

Jacobsen, Buffalo.

Blood and Spinal Fluid Iron Level in Children with Tuberculous Meningitis. M. Lato, Pediatria **60**:585 (Nov.-Dec.) 1952.

The ratio of the iron content of the blood plasma to the iron content of the spinal fluid is normally 4:1. In 13 patients with tuberculous meningitis, the ratio was found to be much higher, namely, 8:1 to 10:1. The iron content of both the blood and spinal fluid of these patients was below normal. This diminution is ascribed to a greater need for iron by the reticuloendothelium of the body tissues, and, especially, of the meninges.

Higgins, Boston.

A Case of Hyperthyroidism in a Premature Infant. V. Jirsova, and V. Brychnac, Pediat. Listy **8**:109 (June) 1953.

Jirsova and Brychnac describe a case of hyperthyroidism in a premature boy. In 3½ months the condition ended in spontaneous cure. The hyperthyroidism probably arose during pregnancy as a result of the maternal thyrotropic hormone affecting the fetus through the placenta. Two years prior to her pregnancy the mother underwent thyroidectomy for toxic diffuse goiter.

From the Authors' Summary.

Diseases of Eye

Pupillary Reflexes in Monozygotic Twins. V. Cima, Riv. oto-neuro-oftal. **26**:287 (July-Aug.) 1951.

Lowenstein described four types of pupillary action, considered to be normal variants and, according to him, hereditary in character. Identical pupillary reactions have been noted by Lowenstein in monozygotic twins. Cima studied three pairs of identical twins in an attempt to corroborate these observations. Pupillary reactions were studied by means of the pupillograph of Borsotti, modeled after Lowenstein's instrument. Only the direct reaction to light was studied. In two of the pairs of identical twins there was a marked difference in the initial size of the pupils, indicating a difference in the tone of the muscles of the iris. A decided difference in the latent period was noted in the third pair. The type of curve was not the same in any pair of identical twins. It was evident the curves were not even approximately superimposed. There was also a difference of degree of the pupillary response in identical twins. These findings do not corroborate the statements of Lowenstein that the pupillary reactions to light are hereditary.

N. Savitsky, New York [A. M. A. Arch. Neurol. & Psychiat.].

Teeth and Dentistry

Biology of the Children of Hopewood House, New South Wales: I. Observations on Dental Caries Extending over Five Years (1947 to 1952). B. Lilienthal, N. E. Goldsworthy, H. R. Sullivan, and D. A. Cameron, M. J. Australia **1**:878 (June 20) 1953.

This is Part I of a series on the biology of a group of 81 children living in an institution under nearly optimal conditions. The present study is devoted to observations on dental caries over a 5-year period. The children ranged in age from 4 to 9 years.

It was found that 63 of the 81 children were free from caries. The average number of caries per child was lower than that for similar children in villages in different parts of the world, being only 0.58 per child. The maximum number of lesions was six. The rate of appearance of new lesions was much lower than that in comparable populations elsewhere.

The outstanding difference between this group and children in the general population was the very low amount of refined sugar in their diet.

McGuigan, Evanston, Ill.

Selenium and Dental Caries. Demetrois M. Hadjimarkos and Clara A. Storvick, J. Pediat. **40**:451 (April) 1952.

The authors suggest that in some unknown manner the trace element selenium, found in some western soils, may contribute to dental caries.

Macdonald, Pittsburgh.

Miscellaneous

Toxic Encephalopathy Occurring During Topical Therapy with Asterol. J. W. Wilson, H. Levitt, T. L. Harris, and E. M. Heilgman, J. A. M. A. **150**:1002 (Nov. 8) 1952.

The authors describe two children in whom the use of Asterol (2-dimethylamino-6-[β-diethylaminoethoxy]-benzothiazole) caused encephalopathic toxicity. The first was a child of 4 years who was treated for a pruritic eruption on his trunk. Nine days after treatment was started

there developed hallucinations and generalized muscle tremors, both tonic and clonic in type. There were no other positive neurological symptoms. Laboratory findings were not significant. The electroencephalographic pattern was not normal; neither did it constitute a definite abnormality.

All medication was stopped, and the tremors and hallucinations gradually cleared in six days. The skin lesion became worse, and after six days Asterol dihydrochloride tincture was again begun. After two days, disorientation and hallucinations recurred. Therapy was stopped, and all symptoms cleared after four days.

The second patient, an infant of 10 weeks, was treated with a 2.5% Asterol cream for lesions involving the trunk and extremities. On the 26th day of treatment, lethargy, followed by generalized convulsions, occurred. The electroencephalogram showed a paroxysmal tracing, but not of the type usually found in idiopathic epilepsy or in cerebral aplasia. Symptoms cleared after seven days.

In order that the occurrence of this alarming, but apparently reversible, neurotoxic reaction may be averted, the authors suggest that it is wise to avoid the use of this medicament with very young children, and they even caution against the frequent use of large quantities over extensive body surfaces in older children.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

NEUROTOXIC SYMPTOMS FOLLOWING USE OF ASTEROL DIHYDROCHLORIDE. J. M. HITCH, J. A. M. A. **150**:1004 (Nov. 8) 1952.

Hitch describes three cases in which neuropsychiatric disorders developed after the use of tincture of Asterol dihydrochloride (2-dimethylamino-6-[β-diethylaminoethoxy]-benzothiazole dihydrochloride). The first patient was 2½ years old. The medicament was applied in enormous amounts and held in close apposition to the skin by an impervious dressing. Symptoms appeared after one week. The second patient was 3 years old, and the scalp lesion was inflamed and excoriated. The neuropsychiatric abnormalities did not appear till the 53d day. In both instances the symptoms appeared suddenly and consisted of muscular spasm, especially of the extremities, visual hallucinosis, and depression of the functions of the sensorium. Spontaneous recovery occurred a few days after treatment was stopped, and no recurrences or sequelae were observed.

The third patient, a boy of 4½ years, had previously had symptoms of psychogenic origin. After being under treatment for 11 weeks with Asterol dihydrochloride tincture for a scalp lesion, he had onset of dysarthria, muscular weakness and incoordination, and vomiting. While his symptoms cleared after cessation of medication, they recurred some five months later, accompanied by emotional difficulties. Symptoms here antedated the use of Asterol and persisted long after discontinuance of its use.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

CONVULSIONS FOLLOWING USE OF ASTEROL DIHYDROCHLORIDE. W. N. FEATHERSTONE, J. A. M. A. **150**:1006 (Nov. 8) 1952.

Featherstone describes an infant aged 4 months to whose skin large quantities of Asterol (2-dimethylamino-6-[β-diethylaminoethoxy]-benzothiazole) dihydrochloride had been applied by an overzealous mother for the treatment of ringworm. After 10 days of treatment convulsions occurred. Physical examination, including neurological and ophthalmoscopic examinations, revealed no other abnormality.

Convulsion cleared after cessation of medication, but at the time of this report the child had not regained his usual alertness. The pattern of this baby's course indicated intoxication as a cause of the convulsions. The author advises caution in the use of Asterol dihydrochloride to prevent excess absorption of it by small children and infants.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

News and Comment

GENERAL NEWS

Specialists Certified by The American Board of Pediatrics, Inc.—The following physicians were certified as specialists by The American Board of Pediatrics, Inc., after examinations held in Miami, Fla., Oct. 9, 10, and 11, 1953:

Ando, Richard Etsuo, New York.
Berglund, Eldon Burdette, Minneapolis.
Birney, Thomas P., Bridgeport.
Block, Bernard, Chicago.
Bohan, Kenneth E., Oklahoma City.
Branch, LeRoy Kilpatrick, Key West, Fla.
Brock, William Michael, Montgomery, Ala.
Busquets, Antonio R., Ponce, Puerto Rico.
Bussman, John Wood, Portland, Ore.
Cannon, Joe Hamilton, (MC), U. S. A. F.
Caplan, Lester H., Baltimore.
Carroll, Oree M., Middletown, N. Y.
Clanton, Benjamin R., Longview, Texas.
Cochran, Winston E., Cambridge, Mass.
Cunningham, Robert Edwin, Jr., Greenville, Miss.
Dean, William Berry, Dallas, Texas.
DeBusk, Franklin L., Pensacola, Fla.
Dietrick, Arthur C., (MC), U. S. A. F.
Doucett, James A., Olean, N. Y.
Edwards, Ray Omer, Jacksonville, Fla.
Engle, Howard A., Miami Beach, Fla.
Ewing, George M., Honolulu, T. M.
Fowler, Robert M., Casper, Wyo.
Forman, Joseph Earle, Greenville, S. C.
Goldwyn, Arthur, Phoenixville, Pa.
Harman, William Elgin, Staunton, Va.
Hirsch, Joseph Rothchild, Baton Rouge, La.
Holdredge, Jean Marie, Wyandotte, Mich.
Hsia, David Yi-Yung, Boston.
Imburg, Jerome, Washington, D. C.
Jaubert, Francis Leon, Jr., Bellaire, Texas.
Johnson, Dale Franklin, Abilene, Texas.
Joslin, Blackburn S., Bethesda, Md.
Joy, Robert Arthur, Manchester, N. H.
Julia, Juan Francisco, New York.
Kaplan, Sidney, (MC), U. S. A. F.
Krivit, William, (MC), U. S. A. F.
Lafferty, John William, Hickory, N. C.
Lambdin, Morris A., Salisbury, Md.
Levkoff, Abner H., Charleston, S. C.
Manning, James Arthur, Baltimore, Md.
Miller, Benjamin M., Brooklyn.
Neustein, Charles, New York.
Newman, Arthur Jerome, (MC), U. S. A. F.
O'Donnell, Vincent Lane, Chevy Chase, Md.
Oleson, Dunlap Wrisley, Sarasota, Fla.
Ordway, Nelson Kneeland, New Orleans.
Penn, Rhesa L., Jr., Midland, Texas.
Perry, Ezra B., Birmingham, Ala.
Pisacano, John Charles, Long Beach, N. Y.
Post, James Matthew, Fort Smith, Ark.
Rappaport, Morris, Bellerose, N. Y.
Ried, Hubert Leo, Houston, Texas.
Riley, Harris DeWitt, Jr., Nashville, Tenn.
Rosenberg, Albert Aaron, Atlanta, Ga.
Roth, Bina, Washington, D. C.
Rudolph, Abraham Morris, Watertown, Mass.
Schapiro, Joseph B., Chicago.
Seanor, Harry Eugene, Rye, N. Y.
Shumway, Clare N., Jr., Miami, Fla.
Sidbury, James Burne, Wilmington, N. C.
Silver, Jonas, Brooklyn.
Simon, Henry Gerson, New Orleans.
Smith, Francis Michael, Thibodaux, La.
Smith, Stewart Phillip, Chattanooga, Tenn.
Smith, Thales Haskell, Norfolk, Va.
Stewart, Roddie L., Birmingham, Ala.
Strain, James Robert, Baltimore.
Talbot, Milton William, Jr., Big Spring, Texas.
Townes, Andrew W., Jr., Orlando, Fla.
Troendle, Francis John, West Point, N. Y.
Uyeda, Iwao, San Francisco.
Vaden, Edwin Booth, Lynchburg, Va.
Waldo, Frank Bell, Birmingham, Ala.
Williams, Kenan Banks, Winston-Salem, N. C.

DEATHS

Death of Prof. Dante Pacchioni.—Prof. Dante Pacchioni died on July 24, 1953, at the age of 81 years. He was Professor of Pediatrics at the University of Genoa from 1912 to 1942, when he retired. He was one of the pioneers of Italian pediatrics. He was largely responsible for the establishing of the Instituti di Clinica Pediatric G. Gaslini, in Genoa.

ANNOUNCEMENT

Fellowship in Pediatric Roentgenology.—Applications are now being accepted for the Fellowship in Pediatric Roentgenology at the Children's Hospital of Cincinnati. The fellowship will be available Jan. 1, 1954, instead of July 1, 1954. Applicants are requested to submit a *curriculum vitae* and three letters of recommendation to Dr. Frederic N. Silverman, Director, Department of Roentgenology, Children's Hospital, Cincinnati 29.

Continuation Course in Child Psychiatry.—A continuation course in child psychiatry for general physicians, pediatricians, and psychiatrists will be presented by the University of Minnesota next Feb. 1 to 5, 1954. The course will consist principally of small-group discussions of common problems led by recognized experts in the field. A minimum of didactic lecture material will be presented. The guest faculty will include Dr. Sherman Little, Director, Orthopsychiatric Department, Children's Hospital, Buffalo; Dr. Mabel Ross, Mental Health Consultant, U. S. Public Health Service, New York, and Dr. Henry H. Work, Assistant Professor of Pediatrics and Psychiatry, University of Louisville School of Medicine. The course will be presented under the direction of Dr. Reynold A. Jensen, Professor, Departments of Psychiatry and Pediatrics, University of Minnesota Medical School. Lodging and meal accommodations are available at the Center for Continuation Study.

Coming Examinations to Be Held by The American Board of Pediatrics, Inc.—The American Board of Pediatrics, Inc., will hold written examinations at selected places on Friday, Jan. 15, 1954. This is the only written examination which will be given during 1954. The schedule for the oral examinations is as follows: Indianapolis, Dec. 4, 5, and 6, 1953; Washington, D. C., Feb. 19, 20, and 21, 1954; Des Moines, Iowa, March 19, 20, and 21, 1954; New York, May 1, 2, and 3, 1954; San Francisco, June 25, 26, and 27, 1954; Chicago, Oct. 8, 9, and 10, 1954; New Haven, Conn., December, 1954.

Books

Brain Surgeon. By Dr. William Sharpe. Price, $3.75. Pp. 271, with no illustrations. Viking Press, Inc., 18 E. 48th St., New York 17, 1952.

There can be no doubt that Dr. William Sharpe was a remarkable man. This was evident in his ability to teach and in his diversified interests. He made his own way through medical school by teaching his fellow students, and in later life he established recreation centers for children and for Negro schoolteachers. In his work, his special interest was the treatment of cerebral palsy. At the ripe age of 70 he writes his autobiography.

He came by an interest in medicine through example. His father was a Presbyterian minister who had six brothers, all of whom were doctors. In his own family, both he and his two brothers were doctors. It is not surprising, then, that he showed superior ability in that field. There is no greater compliment that one student can pay another than to pay him to teach. Dr. Sharpe, during his four years in medical school and his three years of hospital internship, amassed a fortune of $50,000 through tutoring alone. This happy capacity to make both ends meet never left him, so that at the close of his life he was able to make splendid endowments to more than one worthy cause. During his years as a student, he found time to visit Germany and Russia and later graduate as president of his class. Following his internship, he went to the Johns Hopkins University School of Medicine, where he came in contact with Harvey Cushing and the other great men who practiced there during this period. He even served a year as Cushing's assistant resident and has many interesting things to tell about the great man. In January, 1912, he was appointed first professor of surgery at the Harvard Medical School in Shanghai, China. It was during this period that he performed the famous operation on the son of the President of China. The Chinese matriarch was somewhat unhappy about the procedure, but had taken her own precautions. In the event that her boy died, she had arranged for the surgeon's death. However, all went well, and the fee was approximately $50,000. This is an interesting but uninstructive discussion of Chinese medicine of that day.

From the humble beginnings in New York, he joined the New York Polyclinic School and Hospital, and he also assisted the well-known brain surgeon, Charles Elsberg. It was during this period that he first became interested in cerebral palsy, and it was not long before he gave his first paper at the New York Society of Medicine, in 1915. He had operated on 60 patients, of whom 15 had died (25%) and 45 seemed brighter. He attributed cerebral palsy to supracortical hemorrhage due to birth trauma. There was considerable criticism both of the supposed cause of the palsy and of the value of operation. On these points such a presentation would be flatly condemned today. Unfortunately, there was considerable newspaper publicity favorable to a wonderful new method of curing cerebral palsy. Dr. Sharpe, however, persevered with his idea and decided that the supracortical hemorrhage could be drained away before it coagulated over the brain. There then followed a series of routine spinal punctures on infants, and in a total of 500 babies, 9% were found to have blood in the spinal fluid. In some of these babies, he believed, cerebral palsy developed.

In 1926, he went to Chicago and propounded these theories to the Neurological Society and was roundly called down. Obstetrician De Lee seemed to be supporting him, but in reality was probably not. He states finally that he has operated for cerebral palsy in 2,000 cases with a mortality rate of 4 to 5%; in those who died, routine postmortem examinations were performed, and in all of these supracortical hemorrhage was found. There is no report of how the other 95% got along, except that they survived. At this point it is only proper to say that no pathologist today is able to agree with Dr. Sharpe as to the cause of cerebral palsy, and no surgeon today would even consider his method of procedure. Any surgeon who did so would have to produce evidence as to the beneficial results of such treatment. (The reviewer would be glad to supply a list of present-day authoritative reports in this regard.)

However, it is only fair to state that this is precisely Dr. Sharpe's point, namely that no one understands cerebral palsy but him. It is also mainly for the purpose of setting forth his own unique point of view that he wrote the book. So much for cerebral palsy.

The rest of the story has to do with various things—accounts of travel, family life, and exciting experiences and cases, as well as short pale-mauve episodes in the lighter vein. Financially speaking, he seems to have always landed on his feet. With regard to exciting cases, like most doctors, he must have encountered many. It is in this connection that his histrionic ability is clearly shown; certainly no telling point is overlooked. In these dramatic cases, he appears to have snatched glorious victory from the jaws of overwhelming disaster. But in case you think him too omnipotent, and to show you that he is only human, he recounts his two mistakes. One concerns missing a hemorrhage into a tumor, and in the other he operated while somewhat befuddled after a banquet. Most surgeons would be only too willing to "confess" to a longer list than this, which is a commentary from whichever point of view you choose, Dr. Sharpe's or most surgeons'.

The author's view about postmortem examination permits being signed before operation certainly has a good scientific slant, as does his reasoning that one should know all one can about a given case. However, in most surgical practices this attitude might lead to some hesitation on the part of the subject of such proposed operation. His long-sustained notion that if a cancer patient asks directly about his condition he should be told the whole truth is accepted by some. There are others who still disagree with this idea. A few of his other recounted medical experiences seem to be a little too ghoulish for the general public. There are other incidents in which by deception, even to making a clergyman a dupe, he managed to set family problems to rights. In this, as in some medical matters, it must be a blessing to have so few misgivings.

Although Dr. Sharpe was eminently successful in the sense of acquiring a large practice and writing two textbooks, his properties, to a large extent, were turned over to benevolent organizations. One of his estates was made over to the Herald Tribune Fresh Air Fund, an interracial organization for underprivileged children, and the other was transformed into the Hammocks Beach project for the 8,000 Negro schoolteachers of South Carolina. In his boyhood, the doctor had a Negro friend who was a fine intelligent person, but the restrictions were such that the best he could do was run a shoeshine parlor.

Throughout the book there runs a great tolerance and understanding for persons of other races and religious creeds. This admirable characteristic restrains one from speaking out more harshly about his isolated ideas about cerebral palsy. Should the parents of little ones afflicted with this disease read this book and believe its thesis, namely, that cerebral palsy can be prevented in 70% of cases, their soul-searching reflections could only lead to misery. If they further believe that the disease can be alleviated in the manner here suggested, they are doomed to bitter disapointment and finally to utter despair, for there is no truth in it.

The book is easily read and fairly well put together. The author has overcome many of the obstacles in putting the laymen in touch with a notable surgical career. Dramatization and overemphasis are necessarily often present to outline the picture, for surely a matter-of-fact toned-down version would not produce the emotional reaction for which it strives.

Dr. Sharpe is a fine man, a benevolent man, and a capable surgeon, but on one point, at least, a misguided man.

Syndromes pathologiques du nourrisson et de l'enfant. By Robert Clement, Preface by E. Lesné. Price, 4,100 francs. Pp. 767, with 80 illustrations. Masson et Cie, 120 boulevard Saint-Germain, Paris, 6e, 1952.

A good deal of thought has apparently been given to the manner in which the material in this book is presented. It shows a unity with an avoidance of repetition which is often lacking in textbooks compiled by collaborating authors. The material is divided according to the most important symptom-complex or syndrome. Where diseases might be considered under more than one head, excellent cross-references are given. As far as possible, symptoms are considered first with the various conditions which such symptoms might suggest; then the findings and laboratory helps which lead to a definite diagnosis; finally, the therapy, etiology, and prophylaxis

are considered together. Methods of differential diagnosis and treatment are markedly up to date. Almost all the known pathological conditions of infancy and childhood are covered, but there is no heedless elaboration. One has the sense of a greater wealth of knowledge than is here expressed, knowledge attained through large experience as internist and pediatrician. The author has purposely limited his presentation to the most useful concepts.

This should prove to be a valuable book to students, general practitioners, and pediatricians. The style is simple, the French easily readable, and the illustrations unusually good. The index seems adequate. An interesting feature is the absence of any bibliography. While some might consider this a disadvantage, it is also true that the lack may stimulate the reader to use his own initiative in finding original articles, and many of these will be more up-to-date than the references found in most textbooks.

Streptomycin Treatment of Acute Tuberculosis in Children: A Report on the Meeting of Experts Organized by the UNICEF and WHO, Paris, 9-12 February 1950. Price, 400 francs. Pp. 112. Published for the International Children's Emergency Fund of the United Nations by the International Children's Centre, 2 Bis, Avenue du Parc de Passy 16e, Paris, 1950.

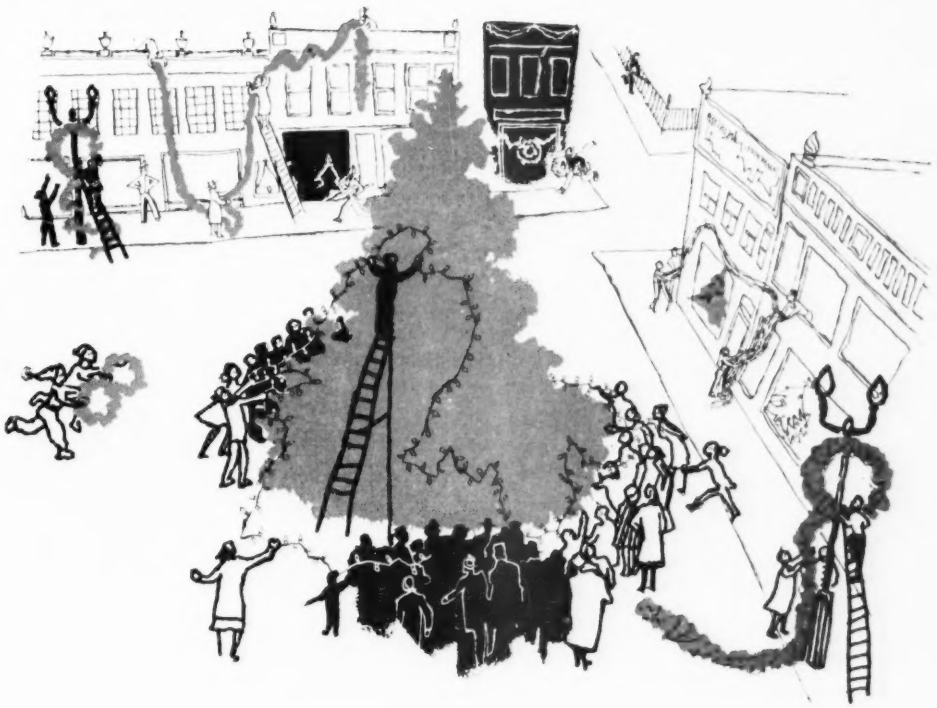
The book contains 16 papers presented by experts from various countries on acute tuberculosis in children. Most of the papers, however, deal with tuberculous meningitis. There is only one paper on miliary tuberculosis and another on alterations of the pathologic anatomy of tuberculous lesions due to the action of streptomycin.

Although the keynote of the book is treatment, the whole field of tuberculous meningitis is covered. There are chapters on diagnosis, cerebrospinal fluid changes, prognosis, ophthalmologic examinations, and sequelae. There is also a chapter on electroencephalography in tuberculous meningitis.

The greater portion of the discussion on treatment is on streptomycin, such as dosage, the route of administration, and the period of treatment.

At the end of the book are general recommendations which reflect the opinion of all the experts in the field. The streptomycin dosage recommended is 20 to 50 mg. per kilogram of body weight in 24 hours, with a daily maximum of 1 gm. Intrathecal administration is advocated, the dosage varying from 20 to 50 mg., according to the age and weight of the patient. The treatment should be continued beyond complete recovery, which is two months after the cerebrospinal fluid has returned to normal. A combination of other antibiotics is also recommended In some cases, suboccipital (cisternal) or ventricular injection is advised. Surgery is to be used in stubborn cases.

It is regretted that the discussion does not contain the opinion of those who administer streptomycin only intramuscularly and those who believe in a shorter course of treatment. It is also regretful that the cisternal route has been agreed upon. In the opinion of the reviewer, this is dangerous. In general, however, the book presents a good discussion of the various phases of tuberculous meningitis.



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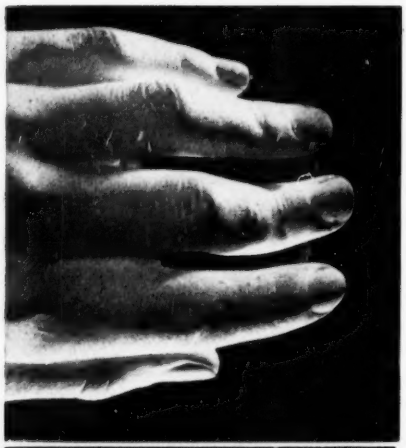

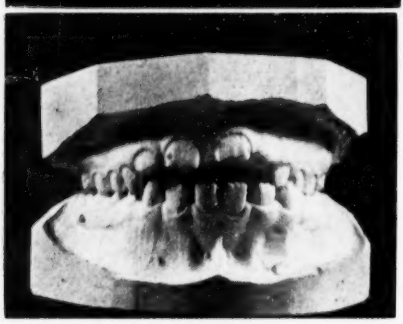

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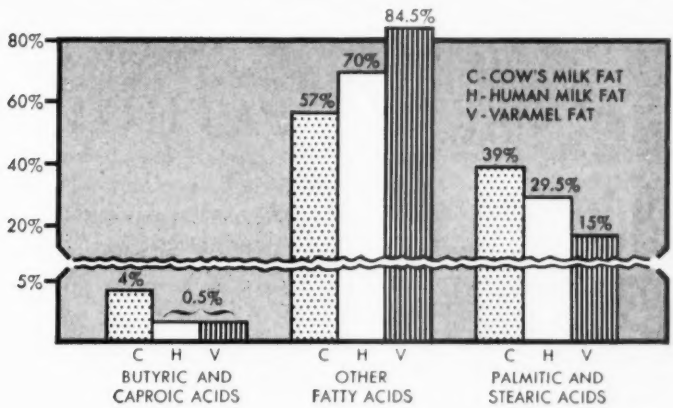

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The Place of Enriched Bread in the Reducing Diet

It is universally acknowledged that the only effective means of weight reduction is restriction of caloric intake. Furthermore, it is acknowledged that no single food can be branded as fattening, that the solution to the problem is sensible limitation of the amounts of all foods eaten.

That enriched bread has a place in the modern reducing diet is evidenced by its inclusion in many weight reduction programs recommended by authorities in the fields of metabolism and internal medicine. Such a diet has recently been included in a pamphlet published by one of the nationwide organizations concerned with national health and the increasing problem of obesity.

This diet, a conventional reducing diet providing 1,200 to 1,400 calories per day, allows a balanced variety of basic foods including bread. Note the sample menu.

Enriched bread is far more than just a carbohydrate food, as is often the mistaken concept. Moreover, in itself, it is not a "fattening food," since only the calorically excessive diet can induce increase in body weight. Three slices of enriched bread provide only 189 calories, yet this amount makes a worthwhile contribution of biologically applicable protein, B group vitamins, and valuable minerals including iron and calcium. Of even greater importance to the person dieting is the gustatory attractiveness which bread lends to the meal.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

BREAKFAST

4 ounces tomato juice
1 boiled egg — 1 slice of toast
1 teaspoon butter — Coffee with milk

LUNCH

Liverwurst sandwich
(1 ounce meat, mustard, lettuce)
Celery — Small bunch grapes
1 cup of milk

DINNER

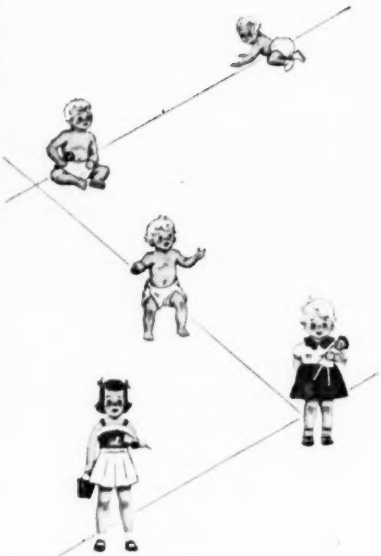
Roast chicken (3 slices, or 3 ounces)
Broccoli — 1 teaspoon butter
Asparagus — Fresh fruit cup
Tomato cucumber salad, vinegar — Coffee or tea with milk

BEDTIME

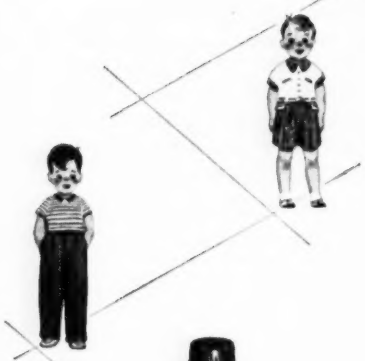
Orange or ½ banana — ½ cup milk

AMERICAN BAKERS ASSOCIATION

20 North Wacker Drive • Chicago 6, Illinois



adequate protection costs so little



No child need be denied protection against the threat of rickets and vitamin A and D deficiencies.

Mead's Oleum Percomorphum is a potent, dependable source of vitamins A and D . . . that can be administered at a cost of about a cent a day.

Specify MEAD'S OLEUM PERCOMORPHUM . . . the pioneer product with 18 years of successful clinical use.

Available in 10 cc. and economical 50 cc. bottles; also in bottles of 50 and 250 capsules.

MEAD

Mead's Oleum Percomorphum

MEAD JOHNSON & COMPANY · EVANSVILLE 21, IND., U.S.A.

SO SIMPLE . . .

even a "first-time father" can prepare it with ease

Though "boiling water" is the extent of his culinary skill, the newest of fathers can, with Similac Liquid, readily prepare a formula closely approximating human breast milk in nutritional quality and digestibility.

AS SIMPLE AS THIS . . .

One part Similac Liquid added to one part sterilized water provides the standard 20 cal./fl. oz. feeding formula.

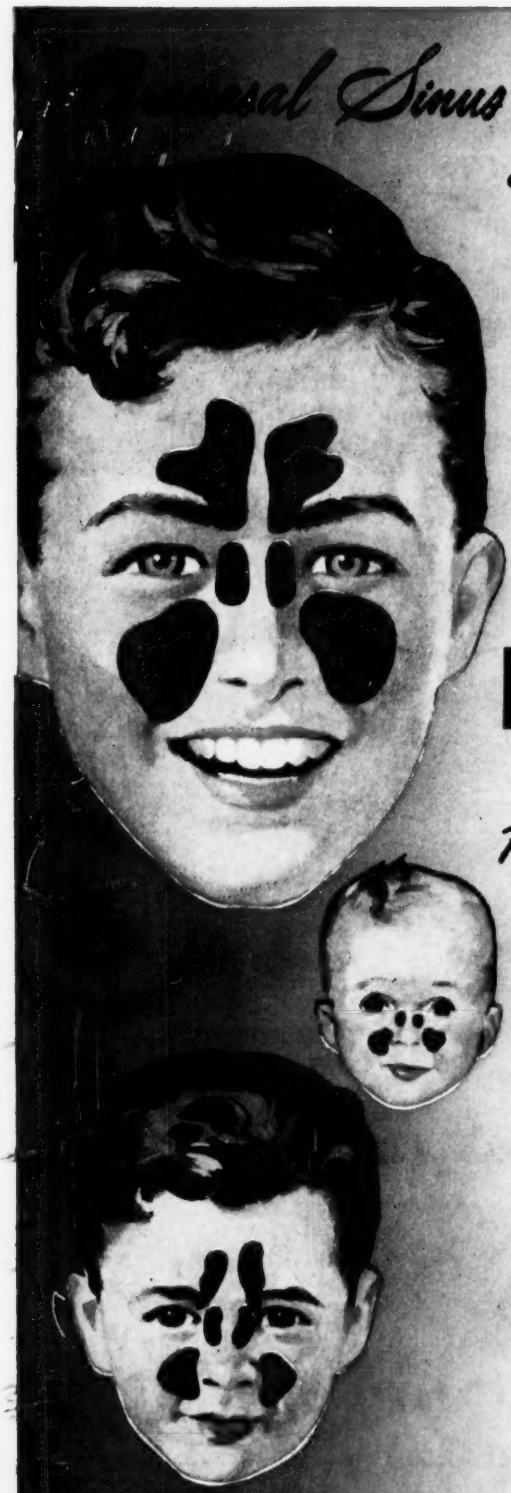
SO SIMILAR TO HUMAN BREAST MILK: *there is no closer equivalent to the milk of healthy, well-nourished mothers in prepared liquid form than*

SIMILAC *Liquid*

Provides: fat, protein and carbohydrate closely approximating the content of mother's milk in quantity and quality; 50 mg. of ascorbic acid per reliquefied quart; vitamin B_{12} and folic acid (naturally occurring, in breast milk quantities); other vitamins in adequate amounts; zero curd tension for easy and quick digestion.

Supplied: *Tins containing 13 fl. oz. Also available: SIMILAC Powder, tins containing 1 lb.*

M & R Laboratories • Columbus 16, Ohio



...nasal Sinus Infection

• IN INFANTS AND CHILDREN—

"In my hands the local treatment giving most satisfactory results is that originated by Proetz . . . displacement irrigation of the sinuses... Neo-Synephrine in normal saline... introduced into each nostril... These drainage and aeration operative procedures do no harm whatever to the physiology of the nose and will prevent more serious and destructive surgery in later life."

Burgess, T. S.: *Jour. Med. Assn. Georgia*, 37:44, Feb., 1948.

Neo-Synephrine®

HYDROCHLORIDE

BRAND OF PHENYLEPHRINE HYDROCHLORIDE

Prompt and Prolonged DECONGESTION

Through persistent decongestive action, Neo-Synephrine affords gratifying relief in colds and rhinitis as well as in sinusitis. It promptly checks mucosal engorgement and hypersecretion, permitting greater breathing comfort that lasts for hours.

Neo-Synephrine is notable for its relative freedom from sting, from compensatory congestion, from appreciable interference with ciliary action.

DOSAGE FORMS:

For nasal use

Neo-Synephrine HCl Solution 0.25% (plain and aromatic), 30 cc. (1 oz.);
0.5% 30 cc. (1 oz.);
1% 30 cc. (1 oz.);
Also ⅛% low surface tension solution 15 cc. (½ oz.).
Water soluble jelly 0.5%, tubes of ⅜ oz.

For ophthalmic use

0.125% (⅛%), low surface tension aqueous solution, isotonic with tears, 15 cc. (½ oz.).

TRADEMARK REG. U. S. & CANADA

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